HYDROAMINATION OF TERMINAL ALLYLIC IMINES, ALLYLIC AMINES, AND INTERNAL AND TERMINAL HOMOALLYLIC AMINES: REGIOSELECTIVE AND REGIODIVERGENT TRANSFORMATIONS

BY

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DISSERTATION

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ABSTRACT

C–N bonds are ubiquitous in organic chemistry. Mild methods that allow for the direct formation of this motif from readily accessible functional groups would represent a powerful advance in organic synthesis. The intermolecular hydroamination of alkenes and amines represents a novel approach towards these disconnections from readily accessible functional groups. This transformation can streamline the synthesis of complex molecules and often allows access to two regioisomers (Markovnikov and anti-Markovnikov) from one starting material.

1,2-diamines are a common motif in many organic molecules. However, their synthesis often involves a lengthy, multi-step synthetic sequence. We report the Rh- and Ir-catalyzed addition of secondary cyclic, secondary acyclic, and primary acyclic (both aryl and aliphatic) amines to allyl amine. This transformation is highly chemoselective, regioselective, functional group tolerant, and can be used to form *trans*-diamines with excellent selectivity. Future directions for this method, including anti-Markovnikov and/or asymmetric hydroamination are discussed.

The anti-Markovnikov hydroamination of aliphatic alkenes is a significant challenge for organometallic chemists. These products are typically formed *via* formal hydroamination. We report the Rh-catalyzed anti-Markovnikov selective hydroamination of homoallylic amines to form 1,4-diamines with electron rich secondary cyclic and acyclic amine nucleophiles. This transformation is tolerant of a variety of substituents on the homoallylic amine and mechanistic studies on these substrates are summarized.

The regiodivergent functionalization of a substrate is a powerful method in organic chemistry; in the hydroamination literature, this transformation typically requires activated alkenes (allenes, dienes, etc.) and is limited in scope. The regiodivergent intermolecular hydroamination of homoallylic amines to selectively form either 1,3- or 1,4-diamines is disclosed. This method features both novel aryl amine nucleophiles and catalysts to form the desired product. This transformation is demonstrated on both terminal and internal alkenes and future directions are proposed.

To Jeremy Menefee

For all of time

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My Husband	Jeremy Menefee

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Chapter 1

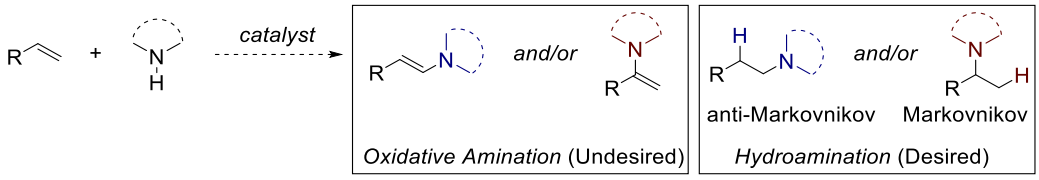
Introduction

1.1 Introduction

C–N bonds are ubiquitous in organic chemistry. Indeed, 57% of all US FDA approved small molecule pharmaceuticals feature at least one nitrogen containing heterocycle[1] and 84% of all FDA approved small molecule drugs contain at least one C–N bond.[1] As such, a method that allows for the rapid incorporation of C–N bonds into target molecules is highly desirable.[2] Traditional methods for the formation of nitrogen moieties historically use pre-oxidized substrates such as carbonyls or alkyl halides as functional group handles;[3] this decreases the step and atom economy for these transformations; hydroamination, the addition of an amine across an unsaturated C–C bond, represents an alternative approach to more traditional methods. This transformation, which features the addition of an amine across an unsaturated C–C bond, couples two readily accessible functional groups with complete atom economy.[4–7] These functional groups are otherwise inert under a wide variety of conditions and obviate the need for pre-functionalization steps. Significant progress has been made since the first report of a transition metal mediated hydroamination reaction by Stern and Spector in 1961.[8] However, there are several significant challenges to intermolecular hydroamination faced by organometallic chemists.

Despite many advances, intermolecular olefin hydroaminations typically have three major limitations: reactivity, chemoselectivity, and regioselectivity. In a hydroamination reaction, the amine is often a better ligand for the metal than the olefin. As such, the reactions generally require a large excess of the alkene coupling partner.[9–13] Second, these methods often suffer from competitive formation of both hydroamination and oxidative amination products (Scheme 1.1).[11,14] Third, a hydroamination reaction can give two possible regioisomers and, typically, in intermolecular hydroamination, either Markovnikov or anti-Markovnikov selectivity is observed and the substrate governs the outcome of the reaction (Scheme 1.1).

Scheme 1.1: Four Products Commonly Observed Under Conditions for Intermolecular Hydroamination.

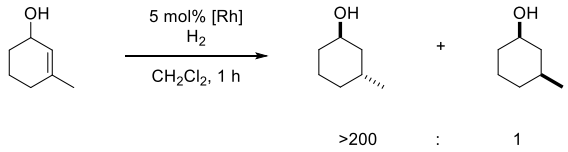


When alkenes bearing aliphatic substituents are subjected to late transition metal mediated hydroamination, Markovnikov products are typically observed.[11,12] When vinyl arenes are subjected to similar conditions, anti-Markovnikov products are usually observed.[14–16] In some cases, judicious selection of conditions can reverse the inherent selectivity of the substrate, although this usually involves modifying the catalyst; Hartwig and coworkers were able to affect the Markovnikov-selective hydroamination of vinyl arenes by adding triflic acid to otherwise anti-Markovnikov-selective conditions.[17,18]

Anti-Markovnikov hydroamination represents a significant challenge to organometallic chemists; accordingly many methods for the formal hydroamination[19] of alkenes have been developed. The two-step aldehyde selective Wacker oxidation/reductive amination of terminal alkenes has been reported by Grubbs and coworkers.[20] Additionally, the two-step hydrozirconation/amination of terminal alkenes was disclosed by Hartwig *et al.*[21] Finally, work originally reported by Lalic and coworkers, and improved and expanded upon by Buchwald, Miura, and Hartwig, features the copper-catalyzed formal hydroamination of terminal and internal alkenes.[22,23] The fact that these methods of formal hydroamination exist as recent reports in the literature, and the caliber of names associated with these reports, demonstrate the extent to which development of a general method of anti-Markovnikov hydroamination would be a significant advance in organic synthesis.

Directed metal-catalyzed reactions are an extremely powerful method for effecting site-selective transformations. The rhodium-catalyzed facially selective hydrogenation of cyclic allylic alcohols was originally reported by Crabtree and coworkers (Scheme 1.2).[24] Here, the alcohol binds to the metal catalysts to effect a diastereoselective hydrogenation reaction with >200:1 selectivity.

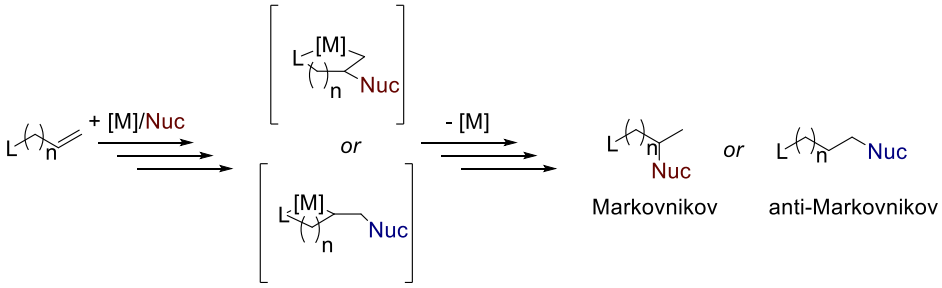
Scheme 1.2: Directed Approach to Hydrogenation of Alkenes.



Similarly, site-selective C–H activation reactions have demonstrated the utility of a Lewis-basic group in enforcing chemoselectivity. Work by Sanford and coworkers has shown the ability of nitrogen containing heterocycles to effect regiodivergent C–H arylation,[25] regioselective C-H fluorination,[26] and regio- and chemoselective C–H oxidation.[27]

In the Hull Group, we sought to obviate issues associated with the intermolecular hydroamination of alkenes by utilizing substrates with Lewis-basic groups. First, these groups will bind to the metal center and increase the effective concentration of alkene at the metal, thus eliminating the need to add an excess of alkene to the reaction. Second, this chelating group enforces a high degree of regioselectivity for either the Markovnikov or anti-Markovnikov product, depending upon the relative stability of the metallacycle intermediate formed upon aminometallation (Scheme 1.3). Additionally, the ability to tune the catalyst to form differently numbered metalacycles should allow for regiodivergent hydroamination.

Scheme 1.3: Accessing the Proposed Metalacyclic Intermediate.



Finally, this directing group should slow the rate of oxidative amination relative to hydroamination; the *syn*-periplanar conformation required for β-hydride elimination should be strained, particularly for endocyclic C–H bonds. We envisioned that this method would allow us to harness the latent functionality embedded in a molecule when synthesizing a target or its derivatives (Figure 1.1).

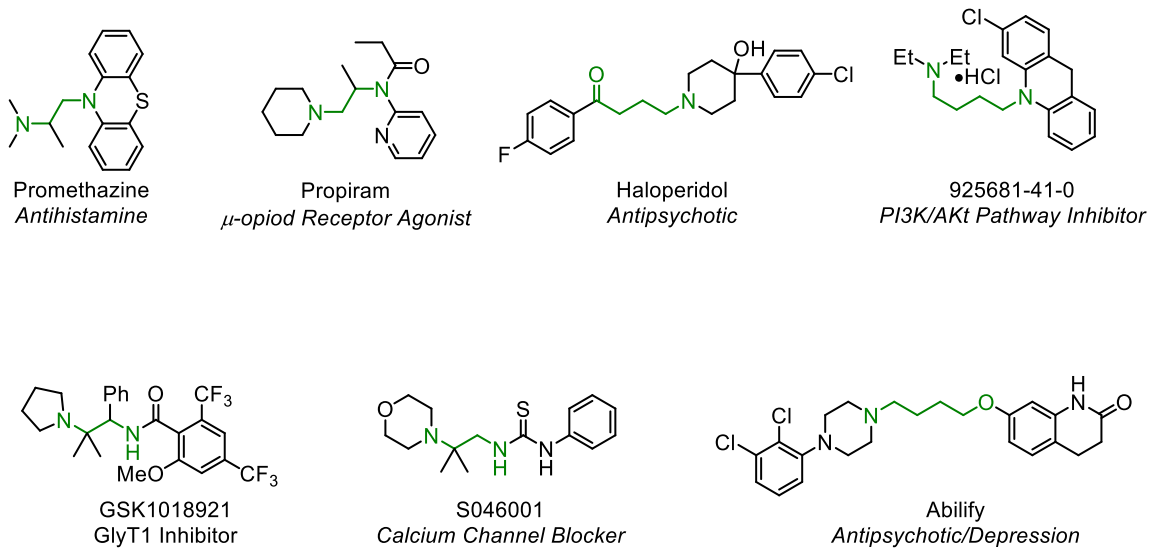


Figure 1.1: Products with 1,2- and 1,4-Disconnections that Could be Formed Through an Intermolecular Hydroamination Reaction.

By developing methods for these unique substrates, we can access a variety of biologically active compounds from a common starting material. This is particular relevant to the pharmaceutical industry as, when developing new drug candidates, medicinal chemists perform structural activity relationship (SAR) studies to determine the efficacy of various derivatives of a compound on a target disease.[28] Often, small structural changes in a drug can have disparate effects on both the disease and the subject being treated (consider that methamphetamine is *N*-methyladerall). The ability to rapidly synthesize many structurally differentiated derivatives of a target molecule would greatly accelerate SAR studies. The feasibility of the methodology developed in the Hull Group is demonstrated with GSK1018921 and derivatives therein; we can access seven distinct products from four common starting materials (Figure 1.2). To date, methodology developed in our group allows rapid access to a variety of common motifs in organic chemistry such as 1,2-;[29] 1,3-;[30] and 1,4-diamines,[30,31] and 1,2- and 1,3-aminothiols.[32]

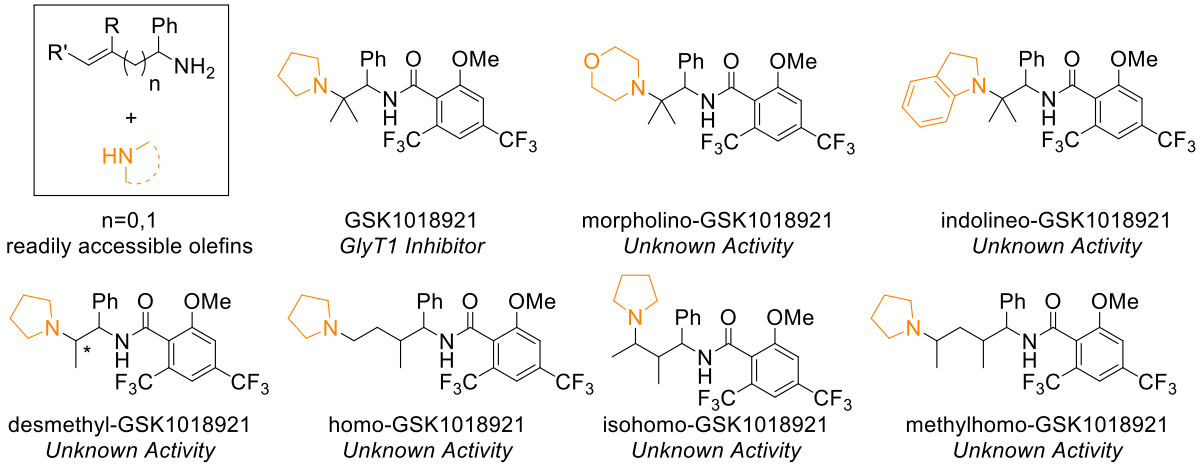
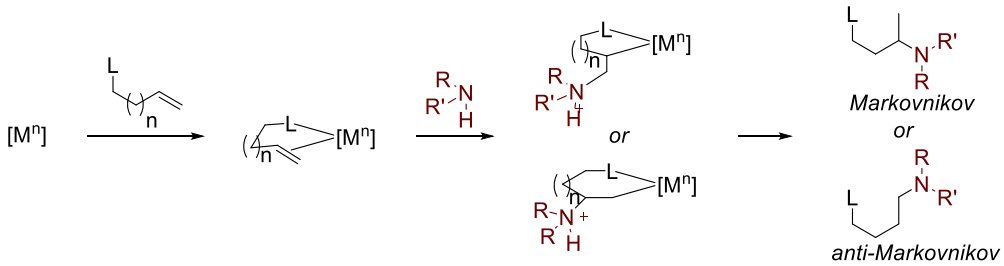


Figure 1.2: The Synthesis of GSK1018921 and its Derivatives Facilitated by an Intermolecular Hydroamination Reaction.

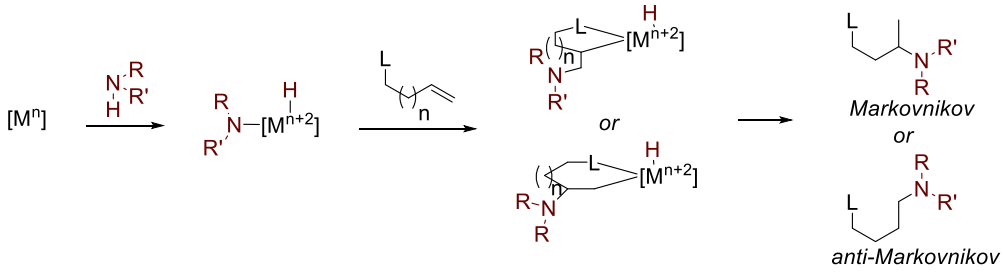
We propose two different mechanisms for the hydroamination reactions developed in our group. With the more electron rich amine nucleophiles discussed in Chapters 2 and 3, we propose that these go through a C–C bond activation mechanism (Scheme 1.4).[7,33–36] In this case, the alkene binds to the metal center and an outer-sphere aminometalation forms a M–C and N–H bond.[37] From here, either direct protonation of the M–C bond by the ammonium to turn over the catalyst or a two-step sequence (featuring proton transfer from the ammonium to the metal followed by C–H bond forming reductive elimination) can occur. Computational studies on related catalysts for intramolecular hydroamination suggest that the latter process is more energetically favorable.[7,34,35]

Scheme 1.4: C–C Bond Activation Mechanism for Intermolecular Hydroamination.



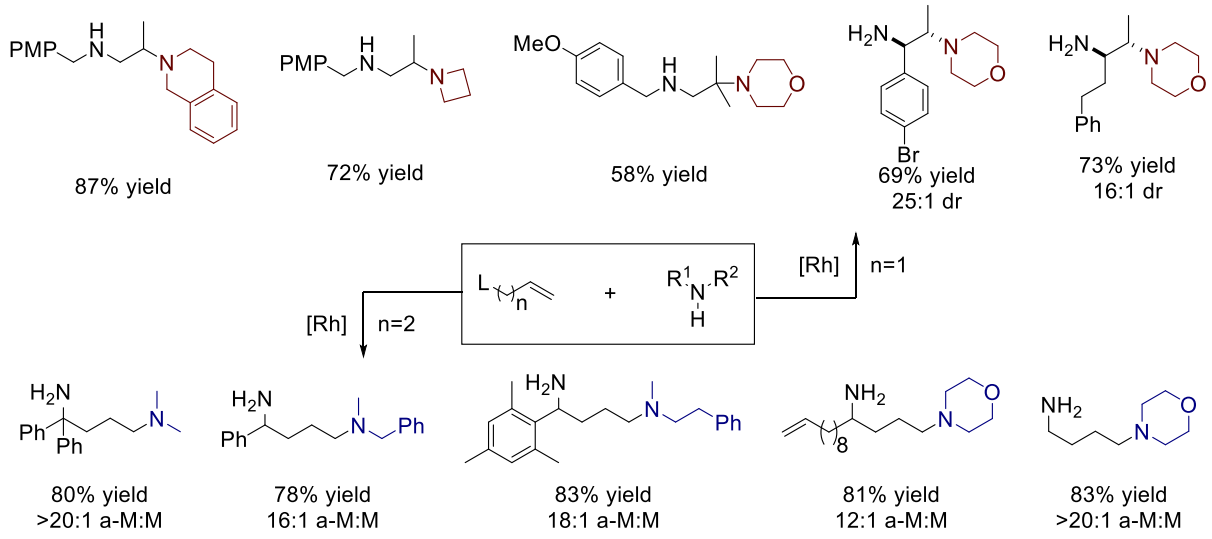
In contrast, the aryl amines discussed in Chapters 2 and 4, unlike more electron rich nucleophiles, appear to proceed through an inner-sphere oxidative addition mechanism (Scheme 1.5).[38–43] Seminal work in this field described the first N–H activation mechanism through stoichiometric studies with an iridium catalyst.[44]

Scheme 1.5: N–H Bond Activation Mechanism for Intermolecular Hydroamination.



Regioselective hydroamination was developed in our group by the enforcement of a five-membered metalacyclic intermediate (Scheme 1.6 and 1.7). By subjecting allylic amines and imines to reaction conditions, 1,2-diamines are obtained; 1,3-diamines would be obtained by forming a four-membered metallacycle. Alternatively, the regioselective hydroamination of homoallylic amines gives 1,4-diamines and not 1,3-diamines, which would be obtained by forming a six-membered metallacycle. In both cases, the selectivity of this transformation is governed by the selectivity of the aminometallation step.

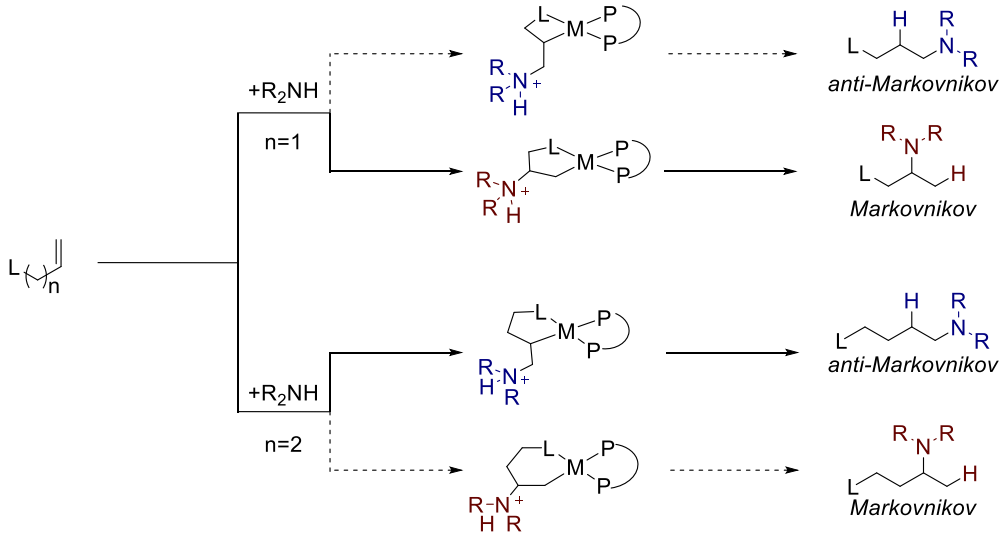
Scheme 1.6: A Representative Sample of Diamines that can be Synthesized *via* a Five-Membered Metalacyclic Intermediate.



The regioselective intermolecular hydroamination of allylic imines and amines was accomplished with a rhodium catalyst with various bidentate phosphine ligands (Chapter 2). Interestingly, while the hydroamination of imines and primary amines with electron rich nucleophiles could be accomplished using the wide bite angle ligand DPEphos, the smaller bite

angle ligand dppp was required for secondary amines.[45,46] This would suggest that subtle differences between the metalacyclic intermediates formed during the reaction require a subtle adjustment of the transition metal catalyst. Additionally, being able to use amines as directing groups (instead of imines) meant that more nucleophilic secondary acyclic and primary amines could be used under reaction conditions. Finally, it is also worth noting that the regioselective hydroamination of allylic amines and imines with aryl amines also gave Markovnikov products; there is a strong preference to form a five-membered metalacyclic intermediate under reaction conditions (Scheme 1.7).

Scheme 1.7: Possible Metallacylic Intermediates for Markovnikov and Anti-Markovnikov Selective Hydroamination.



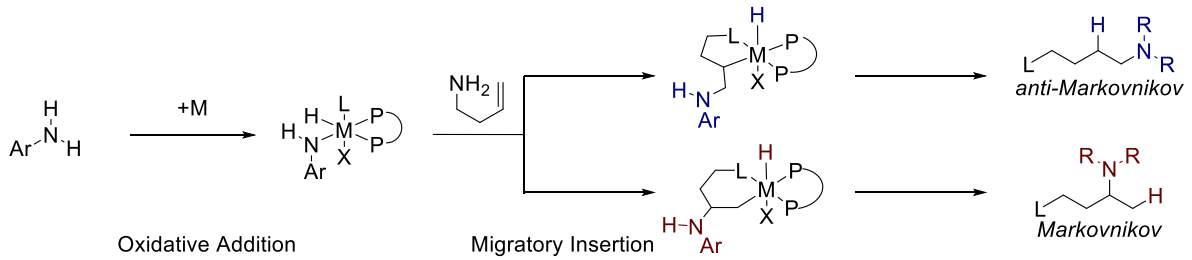
The regioselective hydroamination of homoallylic amines is discussed (Chapter 3). This transformation features electron rich nucleophiles and a Rh^{I} catalyst where different phosphines are required depending on the substitutents on the substrate. α,α-disubstituted substrates give the 1,4-diamine with highest selectivity when DPEphos is used as a ligand (Scheme 1.7). In contrast, anti-Markovnikov products from the hydroamination of α-substituted substrates and homoallyl amine were optimized using dppp. Again, subtle differences in the substrate require different ligands to tune the relative energy difference between the five- and six-membered metalacyclic intermediates.

While the regioselective hydroamination of allylic amines, allylic imines, and homoallylic amines is a powerful method for the formation of 1,2- and 1,4-diamines, this methodology does

not allow access to the other regioisomer (1,3-diamines) of these hydroamination reactions. As such, we set out to develop conditions that would allow for regiodivergent hydroamination.

The regiodivergent hydroamination reported in our group is accomplished by accessing differently numbered metalacyclic intermediates (Chapter 4). Having observed a strong preference to form a five-membered metallacycle with allylic amines (over the significantly more strained four-membered metallacycle), we reasoned that the regiodivergent hydroamination of homoallylic amines may be a more feasible starting point. Here, the choice is between a five- and six-membered metalacyclic intermediate and the difference between these can often be minimized.[47] Through judicious choice of catalyst, ligand, additive, and other reaction conditions, we can access either the Markovnikov or anti-Markovnikov product from the intermolecular hydroamination of homoallylic amines with aryl amines (Scheme 1.8).

Scheme 1.8: General Method for the Regioselective Hydroamination of Homoallylic Amines.



Unsurprisingly, two difference catalysts are required to arrive at these regioisomers. The Rh-catalyzed Markovnikov product is generated with a DPEphos ligand and the stoichiometric addition of $MgCl_2$. It is hypothesized that this Lewis-acid additive can bind to the 1,3-diamine product and allow for catalyst turnover; absent this additive, approximately two turnovers of the catalyst occur in an 18 hour period; about 37 turnovers occur in the presence of the additive. Under anti-Markovnikov selective conditions, $[Ir(cod)Cl]_2$, BINAP, and LiI are combined *in situ* to form the active catalyst. The Lewis-acid additive, in this case, significantly increases the selectivity of the reaction but not the yields. The combination of an Ir catalyst (and not Rh) and iodide additive may allow for a later transition state, which could enhance the selectivity for a metallacyclopentane over a metallacyclohexane (although this is currently under investigation).[48]

While the hydroamination of terminal alkenes is discussed throughout this document, the hydroamination of internal alkenes is a significant challenge. Even methods featuring the formal

hydroamination of internal alkenes require either symmetrical olefins or (in the case where regioselectivity is desired) sterically[49] or electronically[50] biased olefins. We propose that internal alkenes with appended Lewis-basic groups can undergo a regioselective hydroamination reaction. Indeed, initial results demonstrate that a 1,2-disubstituted homoallylic amine can undergo an Ir-catalyzed regioselective reaction to form a 1,4-diamine (Chapter 4). Future directions for this work involve the asymmetric and diastereoselective hydroamination of internal alkenes.

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Chapter 2

Intermolecular Regioselective Hydroamination of Allylic Imines, Allylic Primary Amines, and Allylic Secondary Amines with Electron Rich and Aryl Amines for the Synthesis of 1,2-Diamines

2.1 Introduction

1,2-diamines are common motifs in biologically active compounds, natural products, and ligands (Figure 2.1). Common approaches to this motif involve reductive amination, aza-Henry reactions, nucleophilic displacement (such as an S_N1 or S_N2 reaction,) or the opening of aziridines.[1] Hydroamination, the addition of an amine across an unsaturated C–C bond, can also be envisioned as a complementary approach to 1,2-diamines; using allylic amines or imines as the alkene, this approach is particularly promising if it can be rendered highly chemoselective, enantioselective, and/or diastereoselective.

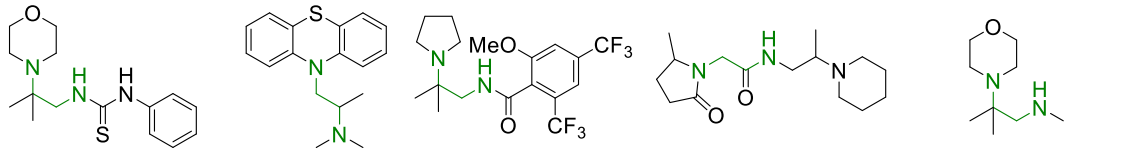
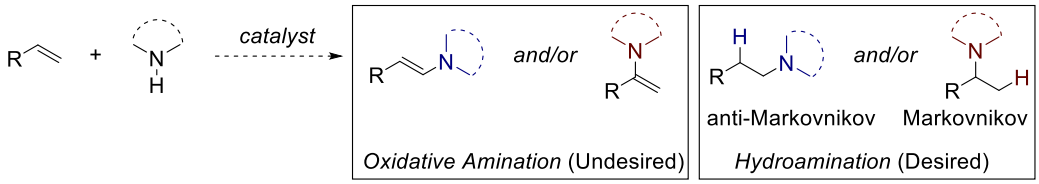


Figure 2.1: Several Biologically Active 1,2-Diamines that can be Accessed with the Methodology Described in Sections 2.2-2.4 of this Chapter.

There have been many reports of the late-transition metal catalyzed hydroamination of alkenes.[2] While these represent a significant advance in the literature, they often face a number of challenges: many reactions are intramolecular,[3–8] require a large excess of alkene relative to amine,[9–13] or form a mixture of both oxidative amination and hydroamination products (Scheme 2.1).[14,15] These transformations are often performed on activated alkenes such as styrenes,[9,10] 1,3-dienes,[16,17] or strained cyclic alkenes.[18–21] Although hydroamination on unactivated alkenes has been reported the scope of these transformations remains limited.[12,14]

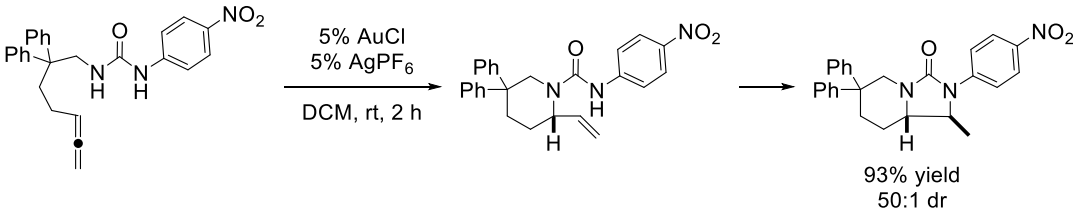
Scheme 2.1: Four Products Commonly Observed Under Conditions for Intermolecular Hydroamination.



To overcome the problems associated with the intermolecular hydroamination of alkenes, we sought to subject an olefin with a distal Lewis-basic group to reaction conditions. This should increase the effective concentration of the olefin at the metal center and obviate the need for an excess of alkene. Additionally, we reasoned that, with the substrate bound in a bidentate κ^3 fashion, the *syn*-periplanar requirement for β-hydride elimination to form oxidative amination products would be significantly strained for endocyclic C–H bonds leading to high chemoselectivity. Current hydroamination methods for the formation of 1,2-diamines do not utilize allylic Lewis-basic substrates and, as such, suffer from some significant limitations.

Hydroamination reactions that allow for the formation of 1,2-diamines have been reported.[22,23] The intramolecular gold-catalyzed dihydroamination of allenes disclosed by Widenhoefer and coworkers allows for the formation of two fused rings from an acyclic starting material (Scheme 2.2).[3] However, this method is limited in that it features a highly activated olefin partner (in the form of an allene) and electron deficient amine coupling partners.

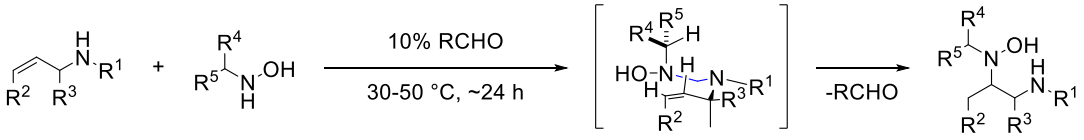
Scheme 2.2: Representative Example for the Gold-Catalyzed Hydroamination of Allenes to Form 1,2-Diamines.



The intermolecular hydroamination of allylic amines with hydroxylamines has been reported by Beauchimin and coworkers in both asymmetric and diastereoselective variants (Scheme 2.3).[24–26] Additionally, a catalytic aldehyde is added to allow for so called "temporary intramolecularity" between the allylic and hydroxyl amine partners. Here, both amine partners condense onto the aldehyde to form an aminal intermediate; this can then undergo a Cope-like

intramolecular hydroamination reaction. The intramolecular reaction is significantly faster than the intermolecular reaction that must occur absent any added aldehyde. Unfortunately with this methodology, activated hydroxylamines must be employed under reaction conditions.

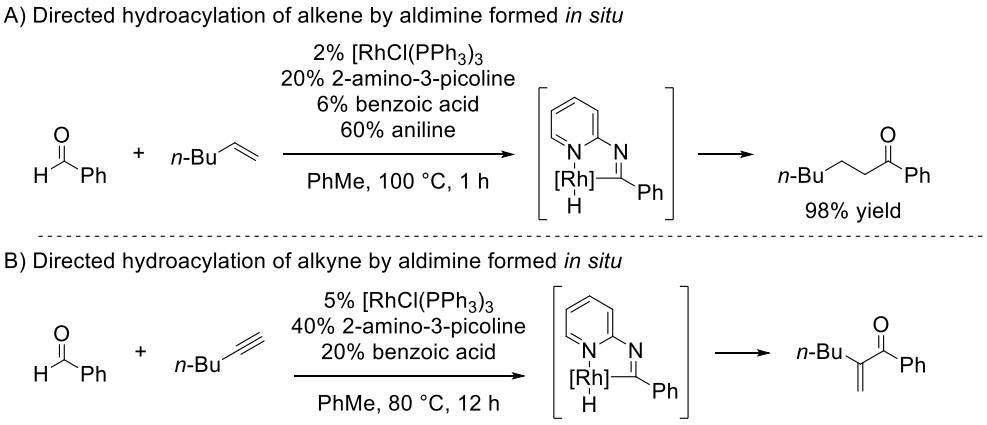
Scheme 2.3: Representative Scope for the Cope-Like Hydroamination of Allylic Amines.



We reasoned that the regioselective hydroamination of allylic imines and amines was an effective method for the synthesis of 1,2-diamines. While alternative methods for the synthesis of this motif have been reported (vide supra), a general method for the intermolecular hydroamination of allylic amines with unactivated nucleophiles has not been previously reported. Additionally, we thought that effecting a directed hydroamination reaction would avoid many of the limitations associated with hydroamination as reported in the literature.

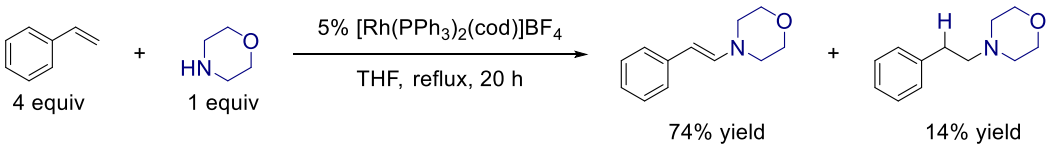
Nitrogen-containing directing groups have been highly effective in Rh-catalyzed transformations.[27,28] Jun and coworkers have demonstrated that the catalytic addition of 2-amino-3-picoline can promote the hydroacylation of aldehydes and terminal alkenes *via* a C–H activation pathway (Scheme 2.4:A).[29,30] Further development of this methodology has extended its scope to the coupling of alkynes and aldehydes (Scheme 2.4:B).[31] It is worth noting that all of these transformations proceed through a five-membered metalacyclic intermediated. Additionally, the nitrogen-containing directing group is effective at suppressing the decarbonylation of the substrate. Having determined that amines were effective directing groups for Rh-catalyzed reactions, we considered previous reports of Rh-catalyzed hydroamination to determine what nucleophiles had a likely chance of success; both electron rich and aryl amines have been reported in intermolecular hydroamination reactions of alkenes.

Scheme 2.4: Representative Examples for the Directed Rh-Catalyzed Hydroacylation of Alkenes and Alkynes *via* a C–H Activation Pathway.



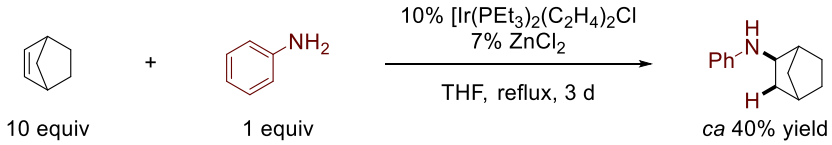
Rh-catalyzed intermolecular hydroamination reactions with secondary cyclic amines have previously been reported.[32,33] Seminal work in this field features the addition of morpholine to vinyl arenes in the presence of a rhodium catalyst as reported by Beller and coworkers (Scheme 2.5).[34] This transformation accomplished the first anti-Markovnikov rhodium-catalyzed intermolecular hydroamination reaction. A subsequent report in the literature by Hartwig and coworkers significantly improved the chemoselectivity of this transformation.[11]

Scheme 2.5: Seminal Report of Rh-Catalyzed Intermolecular Hydroamination of Styrene.



The late transition metal mediated hydroamination of alkenes with aryl amines has been reported.[35–40] Seminal work in this field by Milstein and coworkers utilized a neutral Ir^{I} catalyst to effect the addition of aniline across norbornene (Scheme 2.6).[18] Even with this privileged alkene, used in large excess, the transformation was sluggish.

Scheme 2.6: Seminal Report of the Late Transition Metal-Catalyzed Hydroamination of an Alkene with an Aryl Amine.



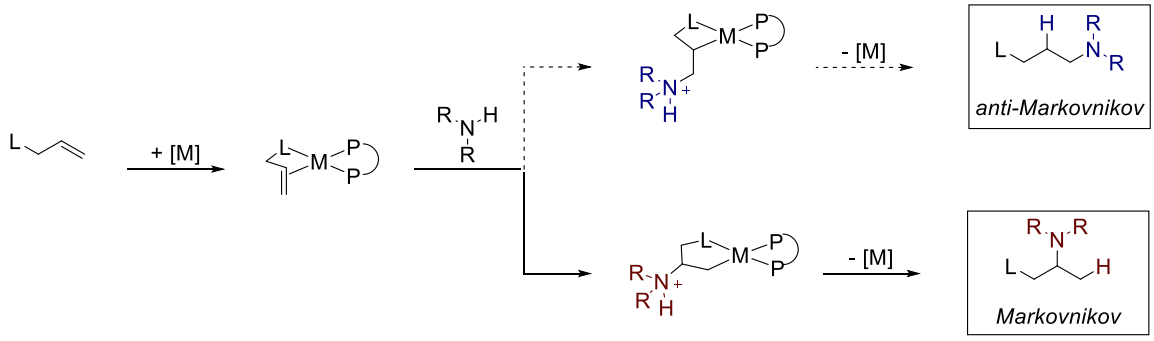
When we began work in this field, there was a clear need for a general method to synthesize 1,2-diamines *via* a hydroamination reaction. Traditional methods for the formation of 1,2-diamines required additional steps to install prefunctionalized groups, such as bromides, ketones, or aziridines, which were then converted into the desired product. Existing hydroamination methods for the formation of 1,2-diamines were limited in scope to either an intramolecular gold catalyzed dihydroamination of allenes or a Cope-like hydroamination with activated hydroxylamines. Alternative methods for hydroamination, while extremely impactful, had significant limitations (vide supra). Hydroamination reactions with both electron rich and aryl amine nucleophiles had been reported. However, these transformations had not yet been applied to substrates containing allylic Lewis-basic groups. It was for these reasons that we sought to develop a highly chemo-, regio-, and diastereoselective method for the Markovnikov hydroamination of allylic amines and imines.

2.2 Hydroamination of *N*-allyl Imines with Electron Rich Nucleophiles

This approach was developed after considering the current limitations of reported hydroamination reactions to form 1,2-diamines; we sought to develop a general method that allows for the chemo-, regio- and diastereoselective formation of these products. Our initial investigations focused on the directed hydroamination utilized in our group. In conjunction with Mr. Andrew Ickes and Dr. Anil Gupta, we examined the ability of *N*-allyl imines to mediate the reaction as these are well known for their ability to bind a metal center.[41] Here, we reasoned that both the *i.* metalacyclic intermediate and *ii.* stereoelectronics should favor formation of Markovnikov products. With these substrates, the reaction is proposed to proceed through either a 5-membered metallacycle (to form Markovnikov products) or a 4-membered metallacycle (to form anti-Markovnikov products). This transformation occurs *via* outer sphere attack by the amine nucleophile on the bound alkene to effect aminometalation (Scheme 2.7). As less strain is associated with the metallacyclopentane than metallacyclobutane intermediate, these substrates

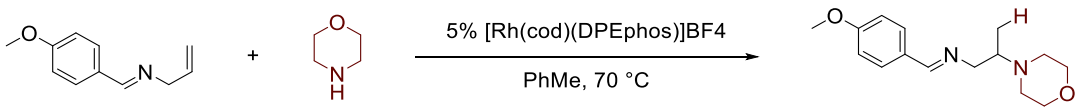
were expected to give rise to Markovnikov products.[42] Additionally, in hydroamination reactions there typically exists a steric preference for the metal center to occupy the terminal position of the incipient alkylmetal species. Bearing these factors in mind, a variety of reaction conditions that would enable successful hydroamination were explored.

Scheme 2.7: Possible Metalacyclic Intermediates from the Intermolecular Hydroamination of Allylic Lewis-Basic Motifs to Form Either Markovnikov or Anti-Markovnikov Products.



Late transition metals are well known for their ability to catalyze intermolecular hydroamination.[32,43] In particular, related work has demonstrated the rhodium-catalyzed addition of cyclic amines to styrenes.[9,11] Our explorations began by applying conditions for the Rh-catalyzed hydroamination of vinyl arenes with electron rich amine nucleophiles to our system; the desired product was obtained by reacting 1 equivalent of **2**, 5 equivalents of *N*-allyl imine **1** and 5% [Rh(DPEPhos)(cod)]BF_4 to obtain the desired product **3** in 57% GC yield (Scheme 2.8). Excitingly, no competing oxidative amination, transfer hydrogenation, or anti-Markovnikov products were observed. With further optimization, yields were significantly improved and an excess of the alkene substrate was not necessary. This is in direct contrast to related transformations that do require an (often large) excess of olefin relative to amine.[41]

Scheme 2.8: Initial Result for the Rh-Catalyzed Addition of Morpholine to Allylic Imine.

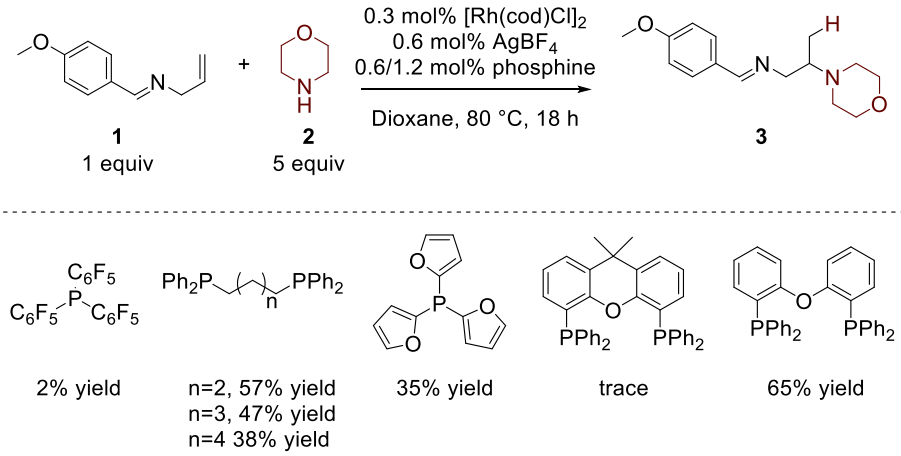


2.2.1 Optimization

After reactivity was observed using the allylic imine and morpholine, a variety of phosphine ligands were screened (Chart 2.1). While σ-withdrawing phosphines such as tris(pentafluorophenyl)phosphine and tri(2-furyl)phosphine were low yielding, bidentate

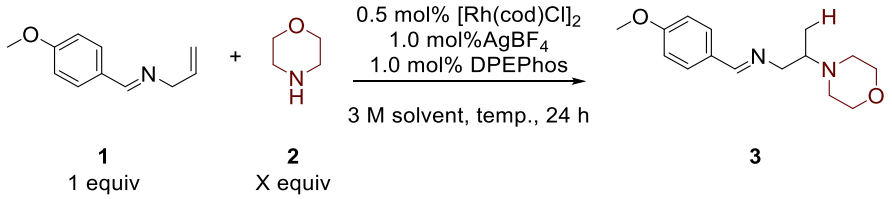
phosphines proved effective and DPEphos proved optimal. Notably, DPEphos is an already well known ligand for hydroamination.[4,11,43,44] Xantphos, a phosphine with a wider bite angle and more rigid backbone than DPEphos, was far less effective at catalyzing this reaction. Dramatic differences between these phosphines have been observed.[45]

Chart 2.1: Summary of Phosphine Ligands Screened to Form 1,2-Diamines



Subsequent optimization of reaction conditions varied temperature, time, and concentration. A representative sampling of conditions screened is summarized (Table 2.1). Excitingly, low catalyst loadings are sufficient for near quantitative yields (Table 2.1, Entry 2). A variety of solvents could be employed under reaction conditions but acetonitrile gave the highest yield. Six equivalents of **2** proved optimal (Table 2.1, Entries 2 and 4). Finally, the reaction could be run at temperatures lower than 60 °C but this significantly slowed the rate of the reaction (Table 2.1, Entry 5).

Table 2.1: Summarized Optimization of Reaction Conditions.



Entry	Solvent	Equiv. morpholine	Temp (°C)	GC Yield (%)
1	Dioxane	8	80	88
2	MeCN	6	60	97
3	MeCN	6	80	93
4	MeCN	5	60	86
5	MeCN	6	25	41

2.2.2 Scope

A variety of secondary cyclic amines were highly effective nucleophiles for this hydroamination reaction; a representative set is shown (Table 2.2). Indeed, morpholine (**4**), piperidine (**5**), 1-methylpiperazine (**6**), pyrrolidine (**8**), tetrahydroisoquinoline (**7**), and azetidine (**9**) are competent nucleophiles for the reaction. However, primary electron rich amines (**10**) (such as *tert*-butyl amine) readily exchange with the imine and are unreactive under reaction conditions. Additionally, secondary aryl amines, such as tetrahydroquinoline (**11**), appear to be too electron poor to undergo the outer sphere aminometalation step at appreciable rates; tetrahydroisoquinoline is a competent nucleophile. Finally, in order to facilitate isolation of the products, the 1,2-aminoimines were reduced with sodium borohydride prior to isolation; while isolated yields are shown below, ^{1}H NMR yields for the hydroamination reaction were recorded.[41]

The functional group tolerance of this transformation was demonstrated by employing a variety of *N*-allyl aldimines and ketimines under reaction conditions (Table 2.3). Indeed, the desired 1,2-diamine is formed in the presence of phenols (**12**), esters (**15**), aryl bromides (**16**), and Lewis-basic groups (**17**). Furthermore, both electron rich (**17**) and electron poor (**14**) aldimines can undergo the reaction. Additionally, both sterically encumbered aldimines (**13**) and ketimines (**18** & **19**) are competent directing groups for the reaction. In some cases, these reactions proceeded so cleanly that column chromatography was not required (**12** & **13**). When this

occurred, the amine was removed under reduced pressure and the products were isolated by filtration through alumina.

Table 2.2: Representative Scope of Amine Nucleophiles Under Reaction Conditions for the Formation of 1,2-Diamines.

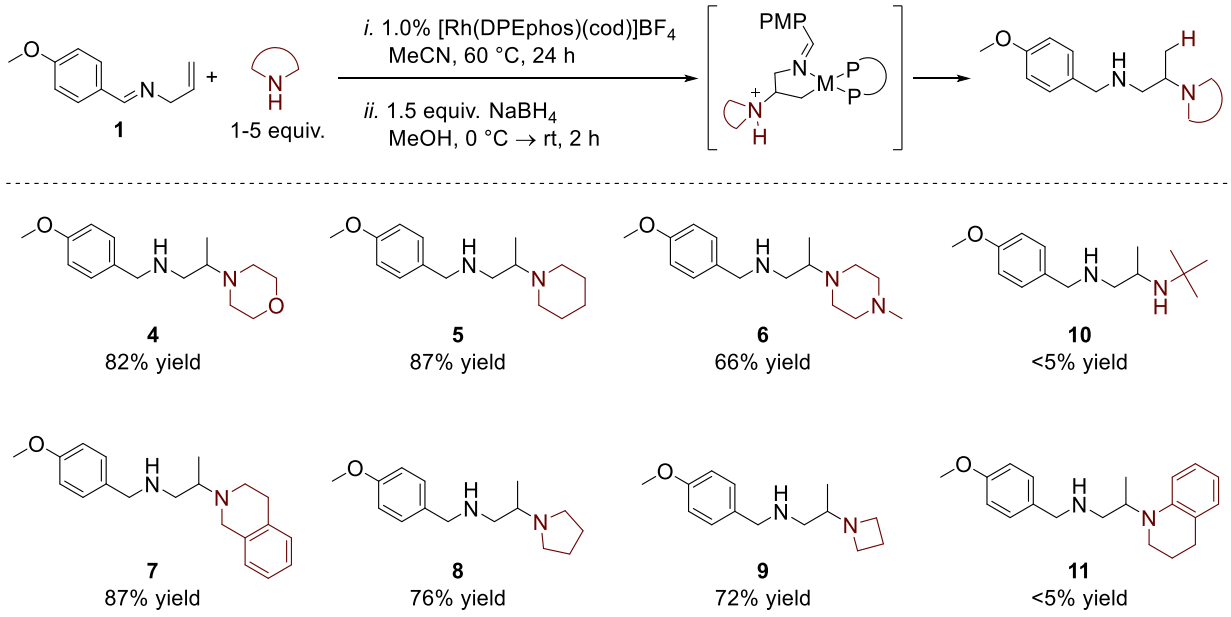
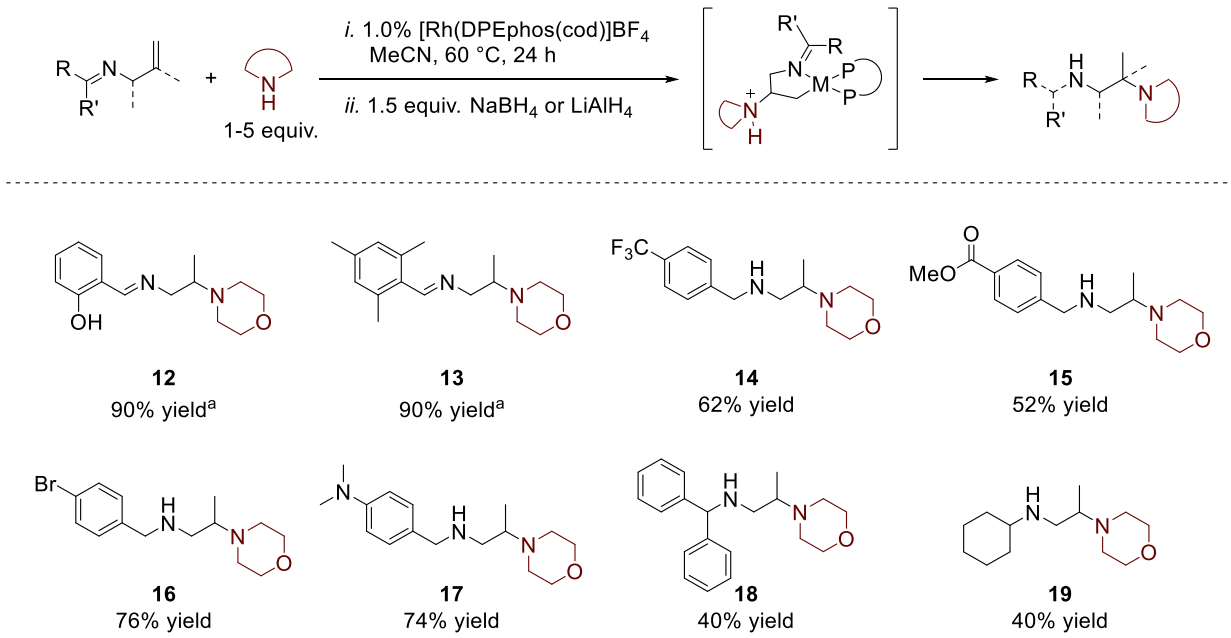


Table 2.3: Representative Scope of Aldimines and Ketimines that Undergo the Hydroamination Reaction.



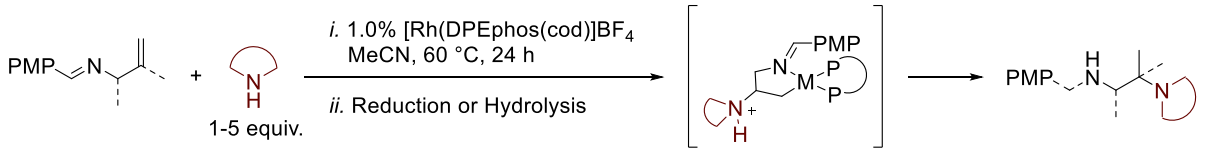
[a]The product was isolated by filtration through alumina without reduction.

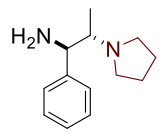
A variety of substituted *N*-allyl imines can undergo the reaction (Table 2.4). When α-substituted substrates are employed under reaction conditions, *trans*-1,2-diamines are observed. These *trans*-selective conditions are not limited to cases where morpholine is used as a nucleophile; pyrrolidine (**21**) can also be used to obtain these products. Additionally, the *trans*-1,2-diamine product is obtained when either aryl (**21**, **23**-**25**) or aliphatic (**22** & **26**) substituents are located at the α-position of the allylic imine; there is good selectivity for this product with both relatively bulky (**23**) and small groups (**22**). Finally, electron donating (**24**) and withdrawing (**25**) substituents are tolerated. The trans-selectivity of this reaction was assigned by comparison of **21** to known compounds in the literature.

Having examined the diastereoselectivity of this transformation with α-substituted substrates, we evaluated β- and γ-substituted allylic imines. While these conditions are not effective for the hydroamination of internal alkenes from γ-substituted stubstrates (the substrate rapidly decomposes *via* a Rh-catalyzed 1,3-hydride shift),[46] this method can be used to form tetrasubstituted centers (**27**) when β-substituted *N*-allyl imines are used under reaction conditions (Table 2.4). At this point, alternative directing groups were examined for their ability to catalyzed the reaction.

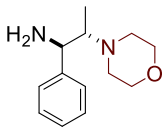
Primary and secondary amines can undergo the intermolecular Rh-catalyzed hydroamination reaction to form **28** and **29** respectively. When subjected to conditions for the hydroamination of allylic imines, the desired 1,2-diamine product is observed with both primary and secondary allylic amines (Table 2.5) although yields are significantly higher with primary amines. It is reasoned that since primary allylic amines are less sterically encumbered than secondary amines they react more rapidly.

Table 2.4: Representative Scope of α- or β-Substituted *N*-Allyl PMP Imines that Undergo the Hydroamination Reaction to Form 1,2-Diamines.

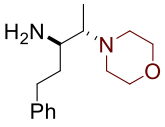




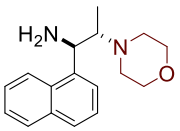
20
50% yield
11:1 dr



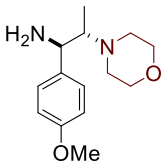
21[a]
79% yield
25:1 dr



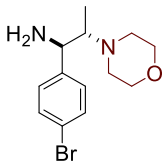
22
73% yield
16:1 dr



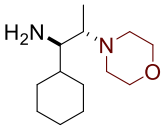
23
78% yield
>20:1 dr



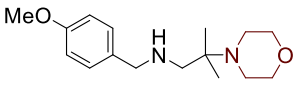
24
80% yield
21:1 dr



25
69% yield
25:1 dr



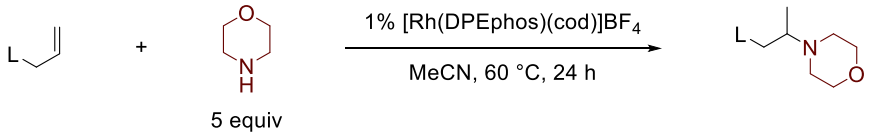
26
58% yield
>20:1 dr

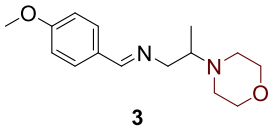


27
58% yield

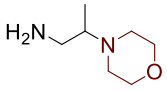
[a]The structure of the trans product was assigned by comparison to known compounds.

Table 2.5: Alternative Allylic Amine Directing Groups that can Form 1,2-Diamines.

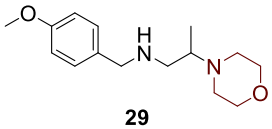




3
94% yield



28
50% yield



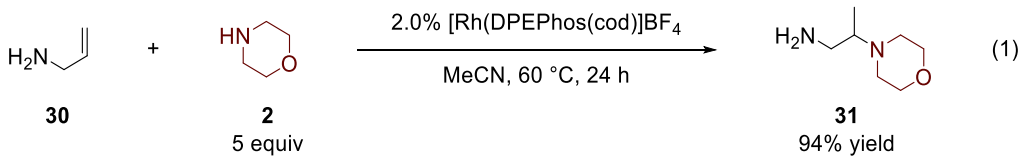
29
trace

2.3 Hydroamination of Primary *N*-allylamines with Electron Rich Nucleophiles

2.3.1 Optimization

The bulk of the work for the hydroamination of primary allylic amines with electron rich nucleophiles was performed by Dr. Anil Gupta and Mr. Andrew Ickes. As such, a truncated discussion of the scope of this reaction is provided for the benefit of the reader. For more detail on this subject, the reader is directed to the chemical literature.[23]

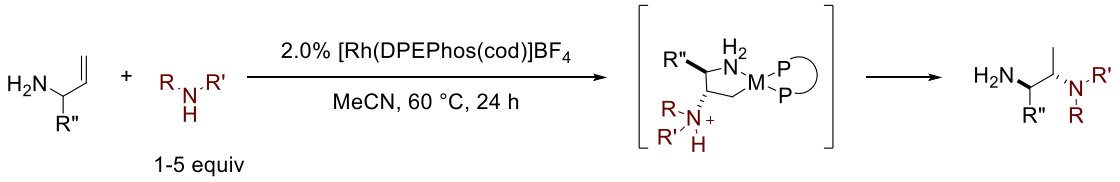
Limited optimization for the hydroamination of allylic amines with electron rich nucleophiles was performed. Good yields (50%) were observed when allyl amine (**30**) and morpholine (**2**) were subjected to conditions previously disclosed for the hydroamination of allylic imines to form **31**. When 2% (and not 1%) [Rh(DPEphos)(cod)]BF_4 is employed under reaction conditions, the desired product (**31)** is formed in 24 h in 94% yield (Equation 1).

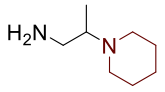


2.3.2 Scope

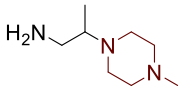
The scope of the reaction was then evaluated (Table 2.6). A variety of secondary cyclic (**33-42**) amine nucleophiles are competent for the reaction. Additionally, for the first time with this methodology, both secondary acyclic (**43**) and primary amines (**44-47**) can form the desired product. This is in direct contrast to the reactivity observed when allylic imines are subjected to reaction conditions; in those cases, the amine exchanges with imine and the desired 1,2-diamine is not observed. Less sterically hindered (such as butyl amine, **44**) and more sterically encumbered amines (such as isopropyl amine, **46**) can both be used. Good diastereoselectivity is observed for this reaction when α-substituted allylic amines (**36-47**) are subjected to reaction conditions and both electron rich (**39)** and electron poor (**41**) substituents are generally well tolerated.

Table 2.6: Representative Scope of Primary Allylic Amines and Amine Nucleophiles that Undergo the Rh-Catalyzed Hydroamination Reaction to Form 1,2-Diamines.

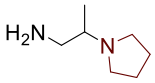




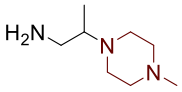
32
60% yield



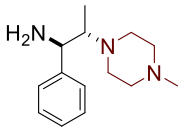
33
63% yield



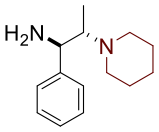
34
45% yield



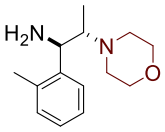
35
63% yield



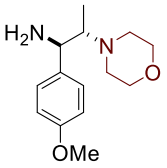
36
71% yield
>20:1 dr



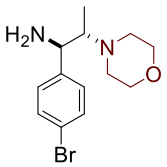
37
65% yield
>20:1 dr



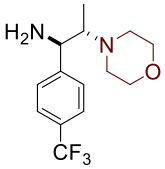
38
76% yield
>20:1 dr



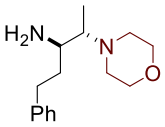
39
77% yield
>20:1 dr



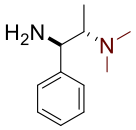
40
77% yield
>20:1 dr



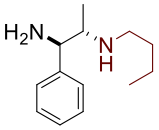
41
82% yield
>20:1 dr



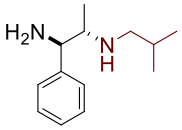
42
75% yield
13:1 dr



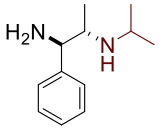
43
74% yield
20:1 dr



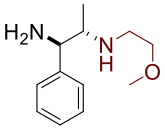
44
64% yield
>20:1 dr



45
56% yield
>20:1 dr



46
55% yield
>20:1 dr



47
71% yield
>20:1 dr

The hydroamination of the allylic amine with another equivalent of allyl amine was not observed under reaction conditions. Interestingly, subjecting allyl amine to reaction conditions absent another primary or secondary amine nucleophile leads to only trace oligomerization. While this is less surprising with α-substituted allylic amines, as a steric argument can be made for why the oligomerization product is not observed, this is more surprising when sterically encumbered amine nucleophiles (such as isopropyl amine) are employed under reaction conditions. Additionally, it is tempting to make an electronic argument for why oligomerization of the starting

material is not observed; the electron withdrawing alkene could lower the nucleophilicity of allyl amine relative to another amine nucleophile. However, inductively withdrawing groups can be present on an amine nucleophile and still give rise to the desired 1,2-diamine. Ongoing work in our lab seeks to understand why more oligomerization of allyl amine is not observed, and if possible, what conditions would give the oligomerized product.

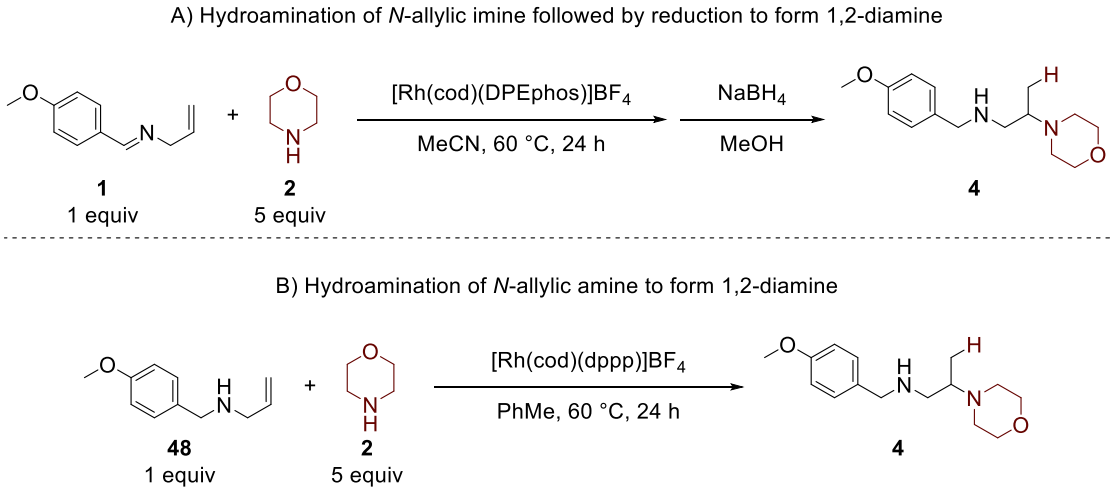
If developed, novel methods for the polymerization of allyl amine may yield materials with properties of interest. Indeed, poly(allylamine hydrochloride) is known as RenaGel and used in the treatment of dialysis patients;[47] material applications of this polymer have also been reported.[48] However, in these cases, the alkene component is polymerized and the amine is left unfunctionalized. Optimizing conditions that allow for the oligomerization of allyl amine with this methodology would allow for a novel method of accessing a constitutional isomer of poly(allylamine hydrochloride).

2.4 Hydroamination of Secondary *N*-allyl Amines with Electron Rich Nucleophiles

2.4.1 Introduction

Having demonstrated that both primary allylic amines and allylic imines were competent substrates for the hydroamination reaction, we sought to broaden the scope of substrates that can undergo the hydroamination reaction, to allow for a greater number of products to be formed *via* this reaction. Additionally, this would reduce the step count for the formation of some 1,2-diamines; previously the allylic imine was subjected to reaction conditions and then reduced prior to isolation. Instead, using this novel methodology, the 1,2-diamine product **4** could be directly isolated by subjecting a secondary allylic amine **48** to reaction conditions (Scheme 2.9). In conjunction with Dr. Anil Gupta and Mr. Andrew Ickes, conditions that allow for this reaction to proceed in good yield were found by varying time, temperature, solvent, and ligand.

Scheme 2.9: Method for the Formation of 1,2-Diamines from (A) the Hydroamination of Allylic Amines Followed by Reduction and (B) the Direct Hydroamination of Secondary Allylic Amines.



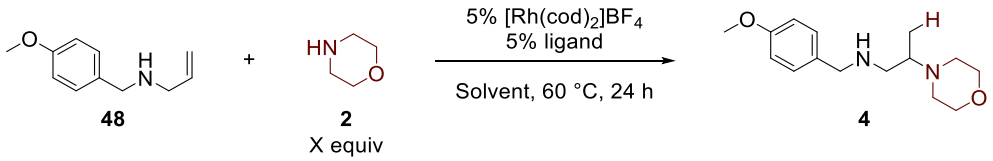
2.4.2 Optimization

Conditions that allow for the hydroamination of secondary allylic amines with electron rich amine nucleophiles were elucidated. Screening was performed using the hydroamination of *para*-methoxybenzylallyl amine with morpholine as a model system (Table 2.7). Excitingly, initial results featuring $[Rh(cod)_2]BF_4$ and DPEphos gave the desired 1,2-diamine in 11% yield.

Smaller bite angle ligands,[49,50] such as dppp and dppb, gave the desired product in greater yields in DME (Table 2.7: Entries 4,5). Further decreasing the bite angle of the ligand by using dppe lead to reduced yields (Table 2.7: Entry 3). Similarly, larger bite angle ligands such as dpppent and dpph were not as effective at catalyzing the reaction (Table 2.7: Entry 6 & 7). A variety of other solvents were then evaluated; the yield of the reaction was significantly increased when toluene was used (Table 2.7: Entries 8-12).

The equivalents of nucleophile were then evaluated. While 5 equivalents of morpholine gave higher yields than 3 or 2, this was not the case for other cyclic secondary amines evaluated under reaction conditions. For example, the highest yields with piperidine and pyrrolidine were observed with 3 equivalents and the highest yield with 1-ethylpiperazine was observed with 2 equivalents. In many cases, yields decreased with higher loading of amine nucleophile.

Table 2.7: Selected Optimization for the Hydroamination of Primary Allylic Amines.



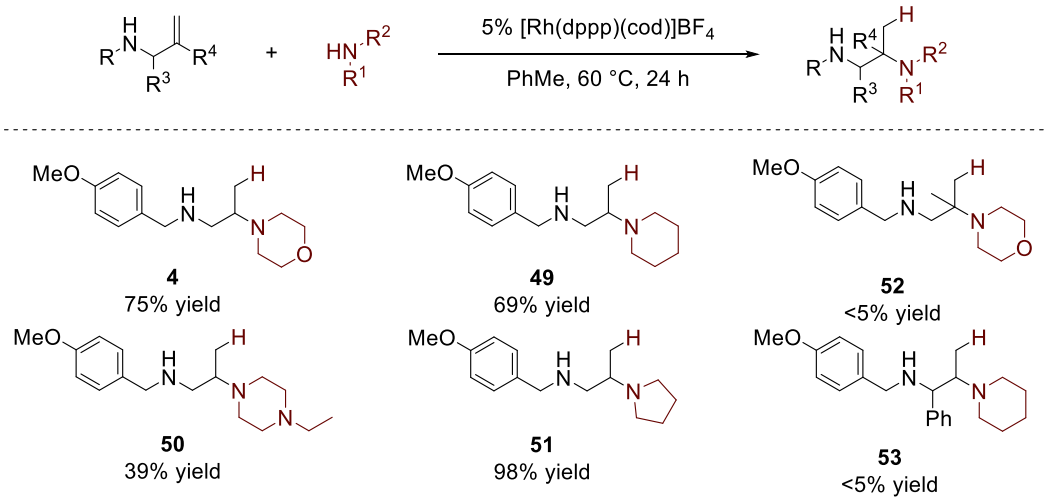
Entry	Ligand	Solvent	Equiv Morpholine	GC Yield (%)
1	DPEphos	MeCN	5	11
2	DPEphos	DME	5	8.0
3	dppe	DME	5	3.3
4	dppp	DME	5	39
5	dppb	DME	5	52
6	dpppent	DME	5	16
7	dpph	DME	5	8.5
8	dppp	MeCN	5	53
9	dppp	PhH	5	59
10	dppp	THF	5	61
11	dppp	Dioxane	5	64
12	dppp	PhMe	5	71
13	dppp	PhMe	3	52
14	dppp	PhMe	2	42
15	dppb	PhMe	5	70

2.4.3 Scope

A variety of secondary cyclic and electron rich amine nucleophiles are competent under reaction conditions (Table 2.8). For example, morpholine, 1-ethylpiperazine, pyrrolidine, and piperidine all give rise to the desired products (**4**, **49-51**). However, when secondary acyclic and primary amines are employed as nucleophiles, the desired 1,2-diamine product is not observed. This may be due to the fact that secondary allylic amines feature directing groups which are sterically encumbered and, with the addition of less hindered, or less nucleophilic amines, the substrate is often not bound to the metal catalyst in a κ^3 fashion. Alternatively, with secondary acyclic nucleophiles, the bound species may not be attacked by the nucleophilic amine at a

significant rate. Sterically encumbered secondary allylic amines also suffer from low conversion; when α- and β-substituted secondary allylic amines are subjected to reaction conditions the desired 1,2-diamine product is not observed (**52** & **53**).

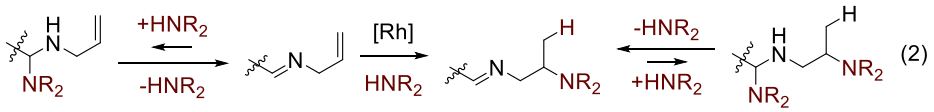
Table 2.8: Representative Scope of Secondary Cyclic Amines that Undergo the Hydroamination Reaction with Secondary Allylic Amines.



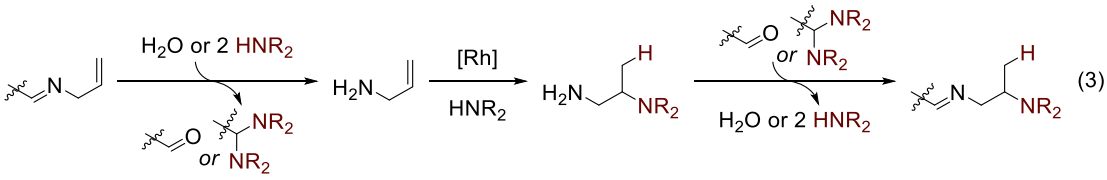
The functional group tolerance of this transformation is still under investigation. However, preliminary results under unoptimized conditions show that aryl bromides, thiophenes, and distal alkenes can all be present under reaction conditions. Ongoing work will evaluate what electronic and steric variations are tolerated.

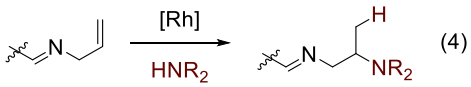
2.5 Mechanistic Studies: Crossover Experiments

This chapter discusses the intermolecular hydroamination of allylic amines and imines. During optimization for the hydroamination of allylic imines, it was found that nucleophilic secondary amines add into the imine directing group (Equation 2).

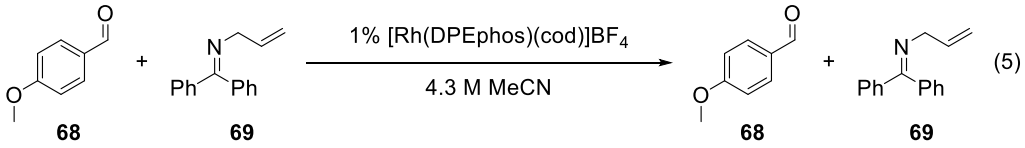


^{1}H NMR evidence of aminal formation was observed under these conditions. Additionally, the ability of *N*-allyl amines to undergo the hydroamination reaction has been discussed (Chapter 2.2-2.4). These facts led to an examination of whether the N-allyl amine (Equation 3) or imine (Equation 4) was the reactive species.

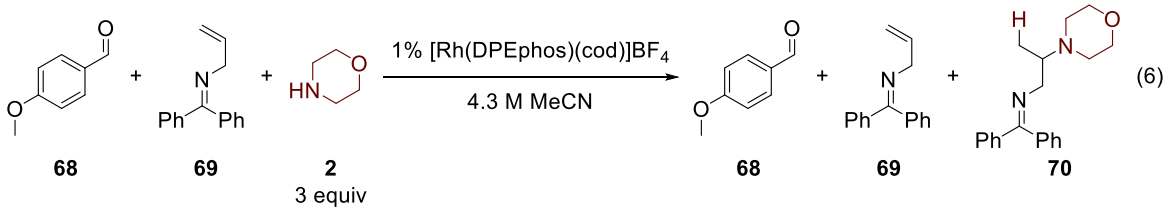


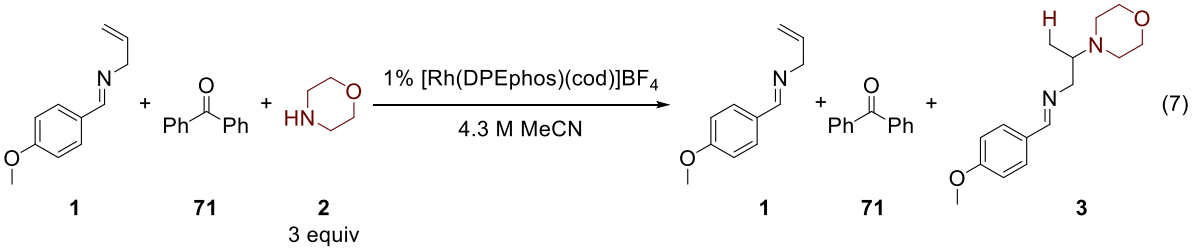


No crossover was observed in the absence of morpholine when *p*-methoxy benzaldehyde and benzophenone *N*-allyl imine were subjected to reaction conditions (Equation 5).



Next, *N*-*para*-methoxybenzyl allyl imine was subjected to reaction conditions in the presence of benzophenone and *N*-allylbenzophenone imine in the presence of *p*-methoxy benzaldehyde. While there should be a bias under equilibrium conditions for the formation of an aldimine over a ketimine, no crossover was observed (Equations 6 & 7).





Due to the fact that only one hydroamination product is formed in both cases, either aldimines or ketimines must be able to undergo the rhodium-catalyzed hydroamination. Experimental data suggests that E/Z isomerization of imines is rapid at room temperature and that rotation around the C–N double bond such that it is eclipsing a C–H single bond is about 2.0 kcal/mole more stable than eclipsing with a C–N single bond[51] although substituents[52] can have a

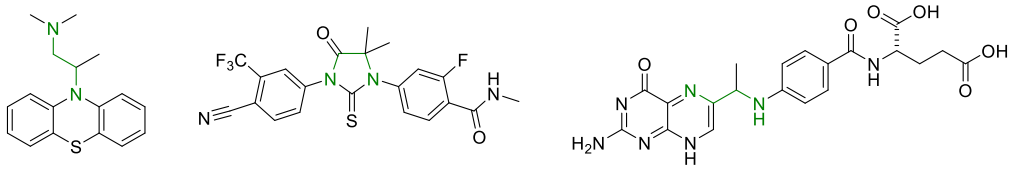
significant effect on these values. This would suggest that an aldimine product is more stable than a ketimine and, if the two possibilities were in equilibrium, competition experiments should always give the aldimine product. Given that this does not occur, these two species are likely not undergoing rapid exchange. This would then show that, when ketimines are subjected to reaction conditions, this is the active species during the hydroamination reaction. These experiments cannot unambiguously show that allylic amines are not the active species when aldimines are employed as substrates.

2.6 Hydroamination of *N*-allyl Amines with Aryl Amines

2.6.1 Introduction

The Markovnikov hydroamination of allylic amines with electron rich primary, secondary cyclic, and secondary acyclic nucleophiles has been thoroughly demonstrated.[23,41] However, the Markovnikov-selective hydroamination of allylic amines with electron deficient amines has not been reported. If this transformation could be achieved, additional pharmaceutically relevant compounds (and their derivatives) could be synthesized (Figure 2.2). Traditional methods for the formation of these products, such as nucleophilic displacement reactions (S_N1 or S_N2), reductive amination, and nucleophilic opening of an aziridine are well known.[1] However, the ability to form these products through a hydroamination reaction would greatly compliment these other methods. Limited examples of the transition metal mediated addition of aryl amines to alkenes have been reported.[35–40] Seminal works are discussed below.

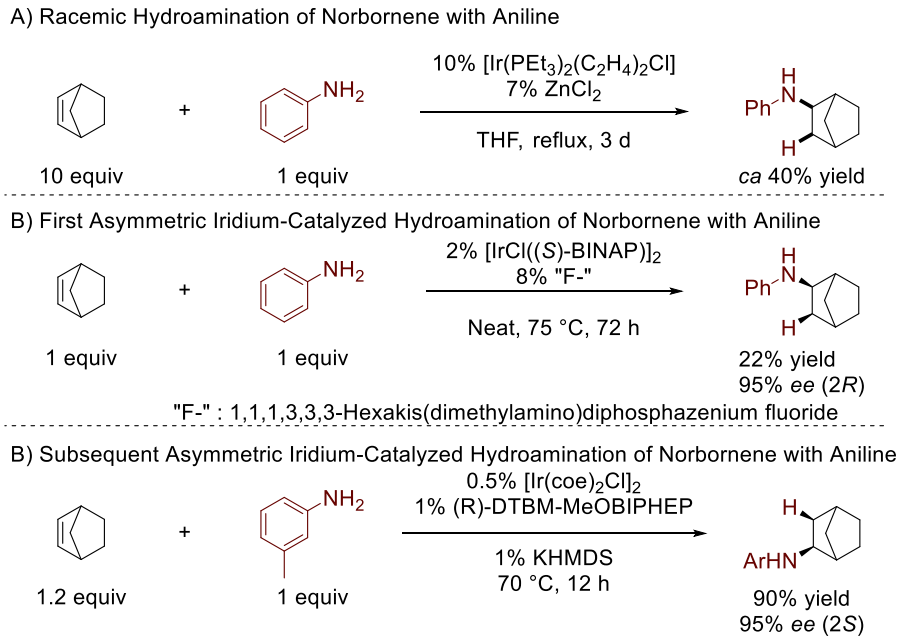
Figure 2.2: 1,2-Diamines that can be Formed From the Markovnikov Selective Hydroamination of Allylic Amines with Aryl Amines.



Aryl amines have been shown to participate in intermolecular late transition metal-catalyzed hydroamination reactions *via* oxidative addition. The first example of this mechanism featured an iridium catalyst and was demonstrated by Milstein and coworkers in 1988;[18] this system focused of the addition of anilines across strained olefins (Scheme 2.10:A). Norbornene

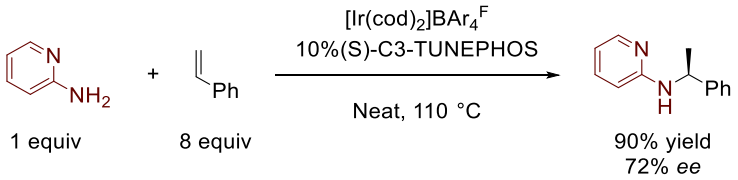
was studied as a model olefin for this transformation. Later work focusing on this system rendered this transformation asymmetric by Togni and coworkers (Scheme 2.10:B).[19] Following this, the scope of this transformation was broadened by Hartwig and coworkers (Scheme 2.10:C).[21] These reactions are typically limited to coupling partners featuring a strained alkene which promotes the migratory insertion step.

Scheme 2.10: Seminal Work for the Hydroamination of Norbornene with Aryl Amines.



Limited examples for the hydroamination of aryl amines across unstrained alkenes have been reported. However, in these cases heterocyclic amines (such as 2-aminopyridine) were required (Scheme 2.11). These heterocycles are proposed to promote oxidative addition into the N–H bond.[53]

Scheme 2.11: Representative Example from the Hydroamination of Vinyl Arenes with Heterocyclic Amines.



Secondary aryl amines have also been demonstrated in intermolecular hydroamination reactions.[15] Indoles have been shown to add across unactivated alkenes (e.g. octene) in the presence of an iridium catalyst. Ethyl acetate proved to be a critical additive in this transformation and was hypothesized to promote M–C/M–N isomerization (Scheme 2.12).

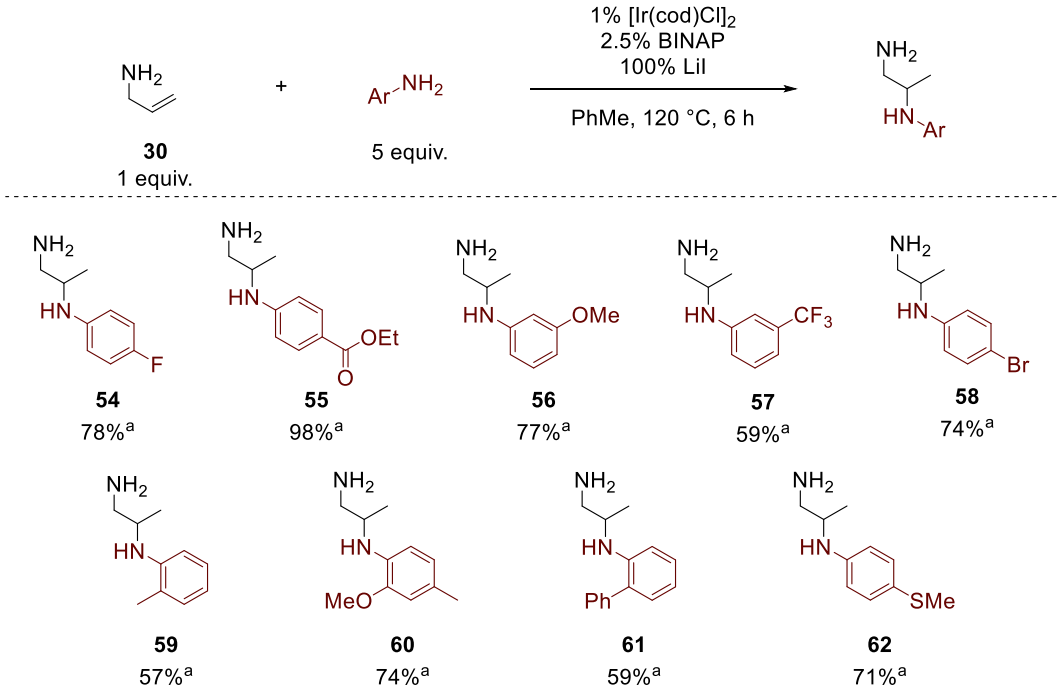
Scheme 2.12: Representative Example from the Hydroamination of Unactivated Aliphatic Alkenes with Indoles.

2.6.2 Optimization and Preliminary Scope

The metal-catalyzed addition of aryl amines to allylic amines represents a previously unreported reaction. While rhodium-catalyzed conditions were examined, the most effective late transition metal for this transformation featured an iridium catalyst. Unsurprisingly, based on literature precedence, biaryl ligands gave the highest yield. When the *in situ* prepared $[Ir(Cl)(BINAP)]_2$ is subjected to reaction conditions, the desired product was observed in trace yield. When one equivalent of LiI is added to these conditions, the desired product is formed in 95% NMR yield. The ability of LiI to significantly increase yields is currently under investigation.[54]

A preliminary scope for this transformation, based on these unoptimized conditions, has been elucidated and ^{1}H NMR yields, relative to an internal standard, are reported (Table 2.9). Both electron rich (**59** & **60**) and electron poor (**54**-**58**) aryl amines are competent under reaction conditions. Potentially reactive functional groups (such as aryl bromides, **58** and ethyl esters, **55**) are well tolerated. Sterically encumbered anilines (2-methyl, **59**, 2-phenyl aniline, **61**, and *para*-cresidine, **60**) are competent nucleophiles.

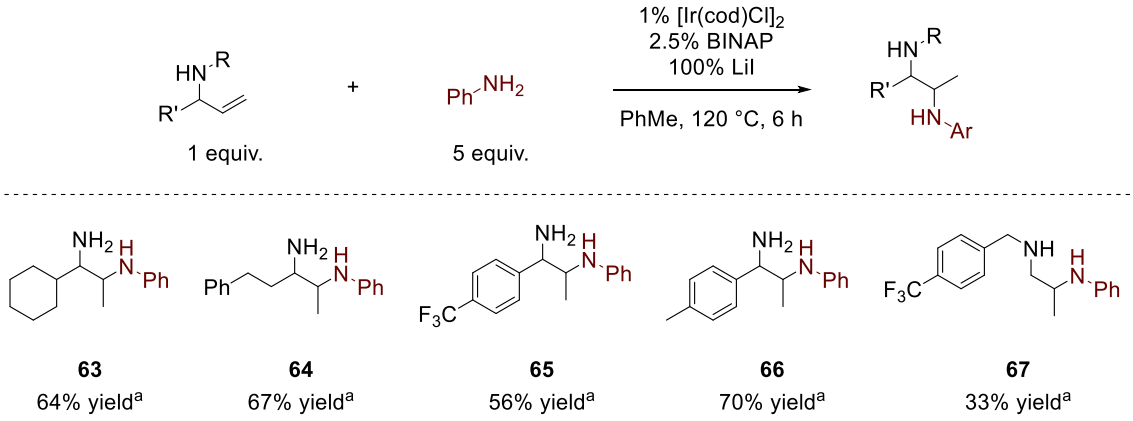
Table 2.9: Representative Sample of Aryl Amines that can Undergo the Ir-Catalyzed Hydroamination Reaction.



[a]Proton NMR Yield reported relative to diphenyl methane as an internal standard.

While the substrate scope of this reaction is currently under investigation, ^{1}H NMR yields with a variety of allylic amines are reported relative to an internal standard (Table 2.10). Substituents bearing either aliphatic (**63** & **64**) or aromatic (**65** & **66**) α-substituents are well tolerated. Both electron rich (**66)** and electron poor (**65)** groups can be located at the α-position. Secondary allylic amines can also undergo the reaction (**67)**, although they do so in reduced yields. It seems likely that exploring alternative bidentate phosphine ligands may significantly increase yields for these substrates.

Table 2.10: Representative Scope of Allylic Amines that can Undergo the Ir-Catalyzed Hydroamination Reaction.



[a]Proton NMR Yield reported relative to diphenyl methane as an internal standard.

2.7 Conclusion

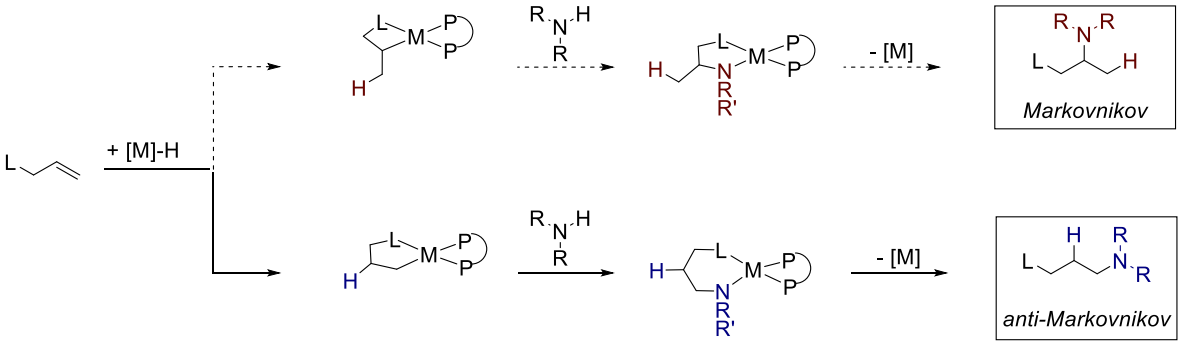
We report the Rh-catalyzed hydroamination of allylic imines, primary allylic amines, and secondary allylic amines with electron-rich nucleophiles to form Markovnikov products and 1,2-diamines. This reaction likely proceeds *via* an outer sphere aminometalation to form a five-membered metalacyclic intermediate and take place with a variety of amine nucleophiles; secondary cyclic amines, secondary acyclic amines, and primary amines can all be employed under reaction conditions. Additionally, a variety of α- and β-substituted allylic Lewis-basic substrates give rise to the desired products. Crossover studies establish imines as competent directing groups for this transformation. Finally, we report preliminary work featuring the iridium-mediated hydroamination of allylic amines with anilines.

The regiodivergent hydroamination of allylic amine or imines remains an attractive challenge for this methodology. Indeed, while it would likely be difficult to access a four-membered metalacyclic intermediate, it may be possible to circumvent this limitation by modifying the catalyst. Previous reports in the literature have demonstrated that the stoichiometric (relative to catalyst) addition of strong acid can reverse the selectivity of a hydroamination reaction.[10]

A similar method could be applied towards the hydroamination of allylic amines or imines. Here, a catalytic cycle that avoids the necessity of accessing a four-membered metallacycle to form

these products could be envisioned (Scheme 2.13). This would involve *i.* migratory insertion by the M–H intermediate to access a five-membered metallacycle and form the desired C–H bond, *ii.* sigma bond metathesis with the M–C intermediate and N–H bond of the amine to form a C–N bond and regenerate the M–H bond and *iii*. ligand exchange to turn over the catalyst.

Scheme 2.13: Rationale for the formation of anti-Markovnikov products with the hydroamination of allylic amines with a metal-hydride catalyst.



Additional work should focus on expanding the scope of alkenes that can undergo this transformation. Noticeably absent from this chapter are internal alkenes; these tend to undergo a Rh-catalyzed 1,3-hydride shift at a far faster rate than the hydroamination reaction.[46,55] Judicious choice of catalyst and ligand, specifically one that slows the rate of β-hydride elimination, may allow for this to occur.

The asymmetric hydroamination of allyl amine to form 1,2-diamines would represent a significant advance for this methodology. Preliminary work by Ms. Jennifer Kennemur and Mr. Evan Vanable has demonstrated the ability of this system to form chiral 1,2-diamines from secondary allylic amines.

Finally, efforts to intercept the M–C intermediate would allow for a three-component coupling reaction to form densely functionalized building blocks. Here, the fact that these substrates access a metalacyclic intermediate should be a significant advantage; this intermediate could be intercepted to form more complex products.

2.8 Experimental Procedure[41]

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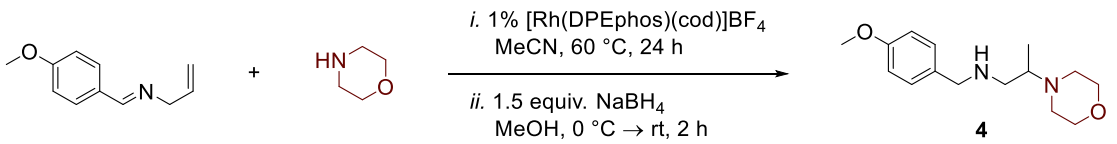
2.8.1 Hydroamination of allylic imines

General Experimental Procedures: All reactions were carried out in flame-dried (or oven-dried at 140 °C for at least 2 h) glassware under an atmosphere of nitrogen unless otherwise indicated. Nitrogen was dried using a drying tube equipped with Drierite™ unless otherwise noted. Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level ~ 0.1 ppm). Column chromatography was performed with silica gel from Grace Davison Discovery Sciences (35-75 μm) with a column mixed as a slurry with the eluent and was packed, rinsed, and run under air pressure. Alternatively, automated columns were performed using a Teledyne ISCO system, employing either Biotage® SNAP Dry Load cartridges (loaded under suction with Davisil Chromatographic Silica Media 35-70 micron mesh), ValueBrand Silica Flash Chromatography Columns purchased from Practichem, or end capped cyano RediSep®Rf Gold columns (20-40 micron mesh) purchased from Teledyne Isco. Samples were eluted using a flow rate of 18–40 mL/min, with detection by UV (254 nm or 280 nm). Analytical thin-layer chromatography (TLC) was performed on precoated glass silica gel plates (by EMD Chemicals Inc.) with F-254 indicator. Visualization was either by short wave (254 nm) ultraviolet light, or by staining with potassium permanganate followed by brief heating on a hot plate or by a heat gun. Distillations were performed using a 3 cm short-path column under reduced pressure or by using a Hickman still at ambient pressure.

Instrumentation: ^{1}H NMR and ^{13}C NMR were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for ^{13}C) or a VXR-500 MHz spectrometer. Spectra were referenced using either $CDCl_3$ or C_6D_6 as solvents (unless otherwise noted) with the residual solvent peak as the internal standard (^{1}H NMR: δ 7.26 ppm, ^{13}C NMR: δ 77.00 ppm for $CDCl_3$ and ^{1}H NMR: δ 7.15 ppm, ^{13}C NMR: δ 128.60 ppm for C_6D_6). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) p (pentet,) m (multiplet,) and br (broad). Coupling constants, J, are reported in Hertz and integration is provided, along with assignments, as indicated. Analysis by Gas Chromatography-Mass Spectrometry (GC-

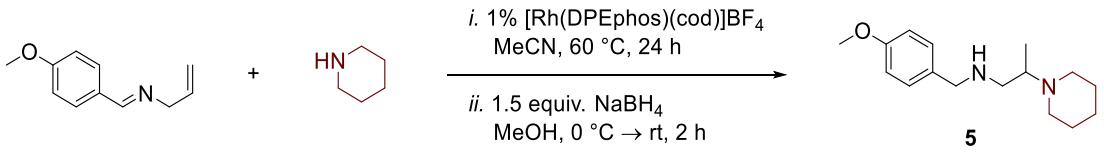
MS) was performed using a Shimadzu GC-2010 Plus Gas chromatograph fitted with a Shimadzu GCMS-QP2010 SE mass spectrometer using electron impact (EI) ionization after analytes traveled through a SHRXI–5MS- 30m x 0.25 mm x 0.25 μm column using a helium carrier gas. Data are reported in the form of m/z (intensity relative to base peak = 100). Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at University of Illinois at Urbana-Champaign. The glove box, MBraun LABmaster sp, was maintained under nitrogen atmosphere. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated Stainless Steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted. All amines (excluding allyl amine) were distilled and degassed by the freeze-pump-thaw method, and were stored over 4 Å molecular sieves under an atmosphere of nitrogen in glove box before use. Allylamine was obtained from Aldrich Chemical Co., Inc. and used as received. All liquid aldehydes were distilled prior to use, and ketones, benzophenone and cyclohexanone, were used as received.



***N*-(4-methoxybenzyl)-2-morpholinopropan-1-amine, 4**: [(DPEphos)Rh(COD)]BF_4 (13 mg, 0.015 mmol, 1.0 mol %), imine (259 μL, 1.50 mmol, 1.00 equiv.) and dry CH_3CN (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (390 μL, 4.5 mmol, 3.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the

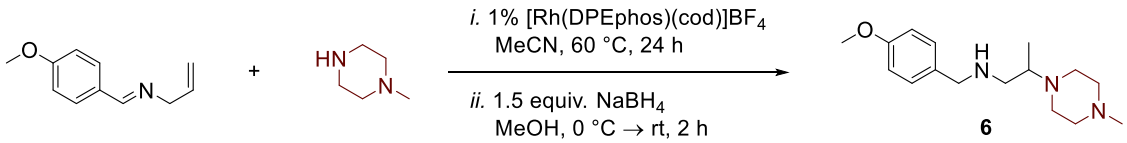
addition of diphenylmethane as an internal standard. To the vial was added p-anisaldehyde (91 µL, 0.75 mmol, 0.50 equiv.) and the mixture was stirred for 2 hours. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (92%) was determined by the analysis of the ^{1}H NMR. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **4** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% NH_4OH : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **4** as a pale yellow oil in 82% yield (323 mg, 1.22 mmol). R_f = 0.55 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.25 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 3.66 (d, J = 12.9 Hz, 1H), 3.64 (d, J = 13.1 Hz, 1H), 3.49 (qdd, J = 11.3, 6.4, 3.3 Hz, 4H), 3.29 (s, 3H), 2.54 (dqd, J = 8.3, 6.6, 4.9 Hz, 1H), 2.43 (dd, J = 11.6, 8.4 Hz, 1H), 2.33 (dd, J = 11.6, 4.9 Hz, 1H), 2.21 (ddd, J = 10.5, 6.5, 3.5 Hz, 2H), 2.07 (ddd, J = 10.6, 6.6, 3.6 Hz, 2H) 1.55 (br s, 1H), 0.70 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 159.0, 133.5, 129.3, 113.9, 67.4, 58.9, 54.7, 53.6, 51.6, 48.8, 11.7 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1906.



5

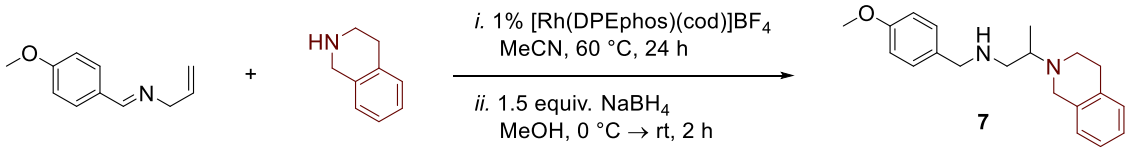
***N*-(4-methoxybenzyl)-2-(piperidin-1-yl)propan-1-amine, 5**: [(DPEphos)Rh(COD)]BF_4 (13 mg, 0.015 mmol, 1.0 mol %), imine (259 µL, 1.50 mmol, 1.00 equiv.) and dry CH_3CN (350 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added piperidine (185 µL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the

addition of diphenylmethane as an internal standard. To the vial was added p-anisaldehyde (91.2 μL, 0.75 mmol, 0.50 equiv.) and the mixture was stirred for 2 hours. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (91%) was determined by the analysis of the ^{1}H NMR. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **5** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% NH4OH : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **5** as a pale yellow oil in 87% yield (340 mg, 1.3 mmol). R_f = 0.63 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.28 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 3.72 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 13.0 Hz, 1H), 3.28 (s, 3H), 2.77-2.70 (dqd, J = 9.2, 6.6, 4.7, 1H), 2.52 (dd, J = 11.3, 9.4 Hz, 1H), 2.39 (dd, J = 11.4, 4.8 Hz, 1H), 2.33 (ddd, J = 10.8, 7.3, 3.4 Hz, 2H), 2.14 (t, J = 7.1 Hz, 2H), 1.86 (s, 1H), 1.44-1.37 (m, 4H), 1.29-1.22 (m, 2H), 0.74 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 159.0, 133.7, 129.4, 113.9, 59.2, 54.7, 53.6, 52.2, 49.3, 26.9, 25.3, 11.3 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{27}N_2O$, 263.2123; found, 263.2130.



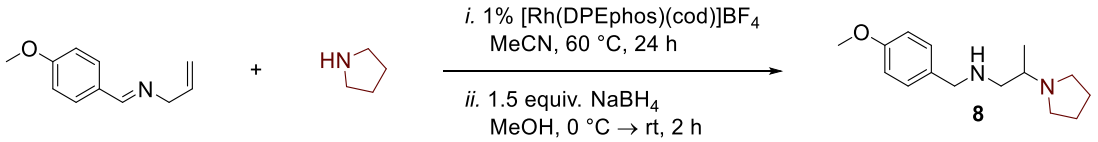
***N*-(4-methoxybenzyl)-2-(4-methylpiperazin-1-yl)propan-1-amine, 6**: [(DPEphos)Rh(COD)]BF_4 (13 mg, 0.015 mmol, 1.0 mol %), imine (259 μL, 1.50 mmol, 1.00 equiv.) and dry CH_3CN (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added 1-methylpiperazine (749 μL, 6.75 mmol, 4.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To the vial was added p-

anisaldehyde (91 µL, 0.75 mmol, 0.50 equiv.) and the mixture was stirred for 2 hours. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (88%) was determined by the analysis of the ^{1}H NMR. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **6** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% NH_4OH : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **6** as a pale yellow oil in 66% yield (274 mg, 0.988 mmol). R_f = 0.42 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.27 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 3.70 (d, J = 13.1 Hz, 1H), 3.67 (d, J = 13.2 Hz, 1H), 3.29 (s, 3H), 2.70 (dqd, J = 8.7, 6.7, 4.8 Hz, 1H), 2.49 (dd, J = 11.6, 8.8 Hz, 1H), 2.46-2.42 (m, 2H), 2.39 (dd, J = 11.6, 4.9 Hz, 1H), 2.30-2.15 (m, 6H), 2.08 (s, 3H), 1.76 (s, 1H), 0.76 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 159.0, 133.7, 129.3, 113.9, 58.5, 55.9, 54.7, 54.7, 53.6, 52.1, 46.2, 11.7 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{28}N_3O$, 278.2232; found, 278.2228



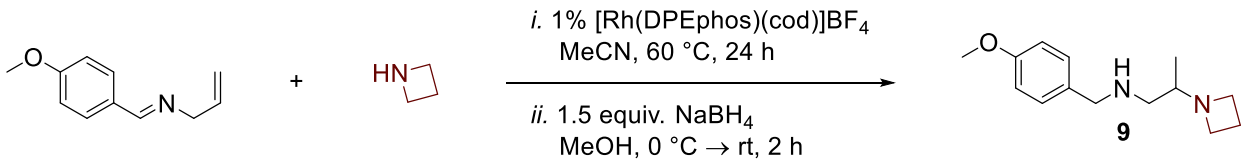
2-(3,4-dihydroisoquinolin-2(1H)-yl)-*N*-(4-methoxybenzyl)propan-1-amine, 7: [(DPEphos)Rh(COD)]BF_4 (13 mg, 0.015 mmol, 1.0 mol %), imine (259 µ, L, 1.50 mmol, 1.00 equiv.) and dry CH_3CN (350 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added tetrahydroisoquinoline (951 µL, 7.50 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction

vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. To the vial was added p-anisaldehyde (91 μL, 0.75 mmol, 0.50 equiv.) and the mixture was stirred for 2 hours. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (91%) was determined by the analysis of the ^{1}H NMR. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **7** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 2% NH_4OH : 2% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **7** as a pale yellow oil in 87% yield (404 mg, 1.30 mmol). R_f = 0.60 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.20 (d, J = 8.7 Hz, 2H), 7.01 (dd, J = 5.5, 3.5 Hz, 2H), 6.94 (dd, J = 5.3, 3.6 Hz, 1H), 6.84 (dd, J = 5.2, 3.7 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 3.69 (d, J = 13.3 Hz, 1H), 3.65 (d, J = 13.3 Hz, 1H), 3.55 (d, J = 14.7 Hz, 1H), 3.43 (d, J = 14.6 Hz, 1H), 3.31 (s, 3H), 2.91-2.84 (m, 1H), 2.64 (t, J = 5.7 Hz, 2H), 2.58 (dd, J = 11.6, 9.0 Hz, 1H), 2.53 (dt, J = 11.1, 5.5 Hz, 1H), 2.43 (dd, J = 11.6, 4.8 Hz, 1H), 2.29 (dt, J = 11.4, 5.8 Hz, 1H), 1.86-1.85 (br s, 1H), 0.77 (d, J=6.6 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 159.00, 136.06, 135.09, 133.62, 129.36, 127.71, 126.81, 125.96, 125.58, 113.89, 58.48, 54.65, 53.53, 52.00, 51.21, 45.51, 30.31, 11.15 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{20}H_{27}N_2O$, 311.2123; found, 311.2125.



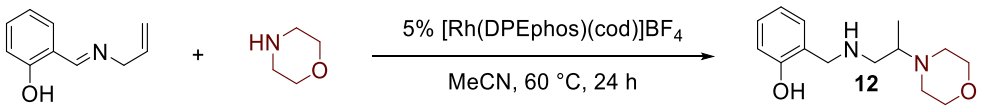
***N*-(4-methoxybenzyl)-2-(pyrrolidin-1-yl)propan-1-amine, 8**: [(DPEphos)Rh(COD)]BF_4 (13 mg, 0.015 mmol, 1.0 mol %), imine (259 μL, 1.50 mmol, 1.00 equiv.) and dry CH_3CN (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction

mixture was added pyrrolidine (185 µL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. To the vial was added p-anisaldehyde (91 µL, 0.75 mmol, 0.50 equiv.) and the mixture was stirred for 2 hours. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (97%) was determined by the analysis of the ^{1}H NMR. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **8** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% NH_4OH : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **8** as a pale yellow oil in 76% yield (282 mg, 1.14 mmol). R_f = 0.61 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.23 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 3.66 (s, 2H), 3.32 (s, 3H), 2.60-2.54 (m, 2H), 2.49 (dq, J = 11.6, 5.8 Hz, 1H), 2.38-2.35 (m, 4H), 1.72 (br s, 1H), 1.53 (m, 4H), 1.04 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 158.99, 133.62, 129.30, 113.85, 57.74, 54.64, 54.01, 53.92, 50.15, 23.80, 15.53 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1960.



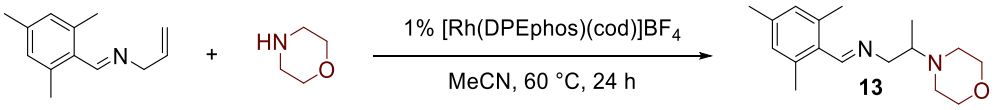
2-(azetidin-1-yl)-*N*-(4-methoxybenzyl)propan-1-amine, 9: [(DPEphos)Rh(COD)]BF_4 (13 mg, 0.015 mmol, 1.0 mol %), imine (259 µL, 1.50 mmol, 1.00 equiv.) and dry CH_3CN (350 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added azetidine (152 µL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the

addition of diphenylmethane as an internal standard. To the vial was added p-anisaldehyde (91 μL, 0.75 mmol, 0.50 equiv.) and the mixture was stirred for 2 hours. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (78%) was determined by the analysis of the ^{1}H NMR. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **9** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 4% NH_4OH : 4% MeOH : 92% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **9** as a pale yellow oil in 72% yield (253 mg, 1.08 mmol). R_f = 0.53 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.26 – 7.18 (m, 2H), 6.85 – 6.75 (m, 2H), 3.62 (s, 2H), 3.31 (s, 3H), 3.15 – 2.75 (m, 4H), 2.44 (qd, J = 11.4, 4.7 Hz, 2H), 2.26 – 2.05 (m, 1H), 1.71 (p, J = 6.8 Hz, 2H), 1.30 (s, 1H), 0.98 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 159.01, 133.55, 129.28, 113.87, 62.83, 54.62, 54.00, 53.51, 52.19, 17.23, 15.21 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1811.



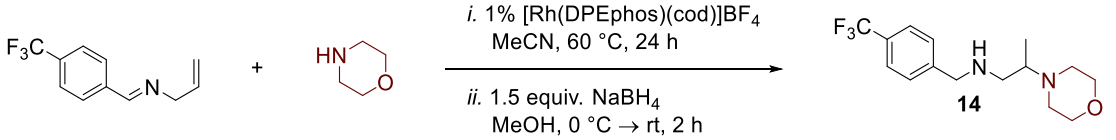
(E)-2-(((2-morpholinopropyl)imino)methyl)phenol, 12: [(DPEphos)Rh(COD)]BF_4 (9.5 mg, 0.011 mmol, 5.0 mol %), imine (36 mg, 0.22 mmol, 1.0 equiv.) and dry CH_3CN (60 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (98 μL, 1.1 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (98%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the original reaction

vial and was rinsed with $CHCl_3$ (2 mL). This mixture was concentrated in vacuo to afford a crude oil. This was run through a short column of basic alumina (eluent 90% hexane : 10% ethyl acetate followed by 100% ethyl acetate). The resulting solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 2 h at 40 °C to afford pure imine **12** as a clear yellow oil in 90% yield (50 mg, 0.20 mmol). In one case where the imine was not pure, automated column chromatography was performed to using a 5.5 g cyano column received from Teledyne ISCO using hexane as the eluent. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.78 (s, 1H), 7.13-7.06 (m, 2H), 6.97 (dd, J = 7.6, 1.6, 1H), 6.72 (td, J = 7.3, 1.3, 1H), 3.57-3.51 (m, 4H), 3.24 (ddd, J = 12.0, 5.8, 1.1, 1H), 3.01 (ddd, J = 11.9, 7.1, 1.1, 1H), 2.43 (sextet, J = 6.5, 1H), 2.24-2.17 (m, 4H), 0.78 (d, J = 6.7, 3H), -0.34 (s, 1H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 165.7, 162.1, 132.5, 131.4, 119.4, 118.6, 117.6, 67.5, 62.1, 60.0, 49.6, 13.3 ppm. HRMS (EI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{20}N_2O_2$, 248.1525; found, 248.1521.

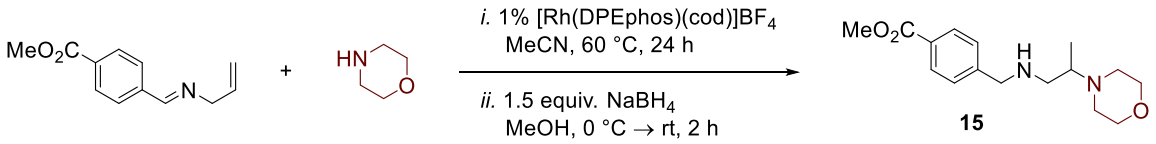


(E)-1-mesityl-*N*-(2-morpholinopropyl)methanimine, 13: [(DPEphos)Rh(COD)]BF_4 (8.4 mg, 0.010 mmol, 1.0 mol %), imine (180 mg, 0.96 mmol, 1.0 equiv.) and dry CH_3CN (260 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (430 µL, 5.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (98%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the original reaction vial and was rinsed with ethyl acetate (2 mL). This mixture was concentrated in vacuo to afford a crude oil. This was run through a short column of basic alumina (eluent 90% hexane : 10% ethyl acetate followed by 100% ethyl acetate). The resulting solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 2 h at 60 °C to afford pure imine **13** as a clear yellow oil in 90% yield (237 mg, 0.862 mmol). ^{1}H NMR (C_6D_6, 500 MHz): δ 8.43 (s, 1H), 6.74 (s, 2H), 2.79 (sextet, J = 6.2, 1H), 2.43 (s, 6H), 2.38 (t, J = 4.6, 4H), 2.11 (s, 3H), 1.02 (d, J = 6.7, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 161.0, 138.6, 137.9, 131.6, 129.9, 67.7, 66.0, 60.5,

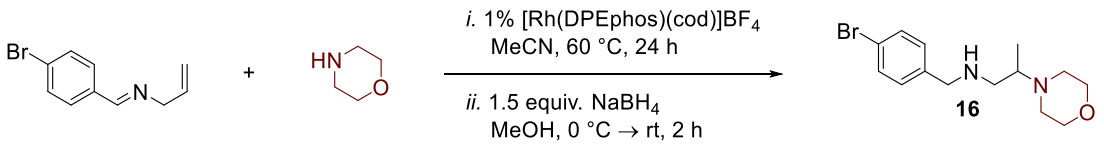
49.9, 21.21, 21.17, 13.8 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{17}H_{27}N_2O$, 275.2123; found, 275.2120.



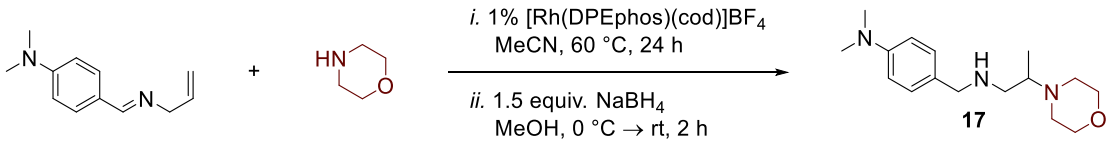
2-morpholino-N-(4-(trifluoromethyl)benzyl)propan-1-amine, 14: [(DPEphos)Rh(COD)]BF_4 (5.7 mg, 0.0068 mmol, 1.0 mol %), imine (146 mg, 0.683 mmol, 1.00 equiv.) and dry CH_3CN (180 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (296 μL, 3.42 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetrachlorobenzene as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (86%) was determined by the analysis of the ^{1}H NMR. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (39 mg, 1.0 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **14** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 1% NH_4OH : 99% $CHCl_3$ to 1% NH_4OH : 1% MeOH : 98% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **14** as a pale yellow oil in a 62% yield (127 mg, 0.420 mmol). R_f = 0.50 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.40 (d, J = 8.0, 2H), 7.20 (d, J = 7.9, 2H), 3.56-3.47 (m, 6H), 2.52 (dq, J = 13.2, 6.6, 1H), 2.33 (dd, J = 11.6, 8.6, 1H), 2.24 (dd, J = 11.3, 4.4, 3H), 2.11 (ddd, J = 10.5, 6.5, 3.5, 2H), 1.85 (s, 1H), 0.72 (d, J = 6.6, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 145.99, 129.18 (q, J CF = 32.1), 128.46, 125.40 (q, J CF = 3.8), 125.17 (q, J CF = 271.5), 67.55, 59.09, 53.50, 51.92, 48.99, 11.74 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{22}N_2OF_3$, 303.1684; found, 303.1670.



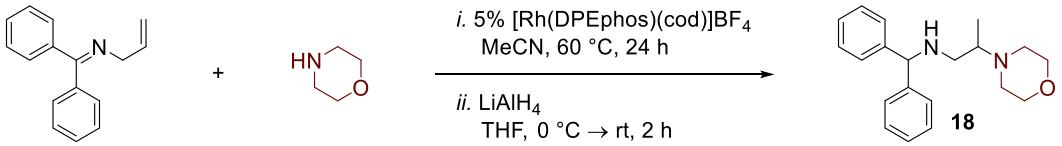
4-(((2-morpholinopropyl)amino)methyl)benzoate, 15: [(DPEphos)Rh(COD)]BF_4 (8.1 mg, 0.0097 mmol, 1.0 mol %), imine (178 mg, 0.967 mmol, 1.00 equiv.) and dry CH_3CN (254 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (418 μL, 4.84 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (88%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (55 mg, 1.5 mmol, 1.5 equiv) and MeOH (3 mL). The flask containing the reducing agent was brought to 0 °C and the solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and was washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **15** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 2% NH_4OH : 98% $CHCl_3$ to 2% NH_4OH : 2% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **15** as a pale yellow oil in 52% yield (132 mg, 0.451 mmol). R_f = 0.67 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 8.14 (d, J = 8.2, 2H), 7.29 (d, J = 8.1, 2H), 3.59 (s, 2H), 3.56-3.47 (m, 7H), 2.55-2.49 (m, 1H), 2.35 (dd, J = 11.6, 8.5, 1H), 2.23 (ddd, J = 18.7, 8.9, 4.1, 3H), 2.09 (ddd, J = 10.6, 6.5, 3.5, 2H), 1.92 (s, 1H), 0.71 (d, J = 6.6, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 166.7, 147.0, 130.0, 129.5, 128.2, 67.5, 59.1, 53.7, 51.8, 51.6, 48.9, 11.8 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{25}N_2O_3$, 293.1865; found, 293.1858.



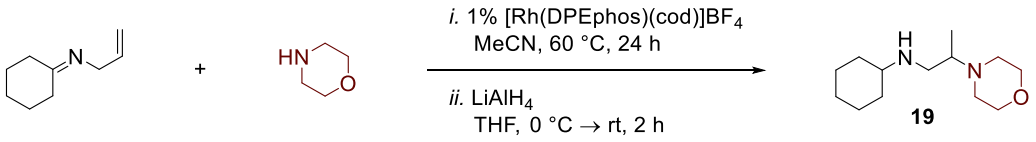
N-(4-bromobenzyl)-2-morpholinopropan-1-amine, 16: $[(DPEphos)Rh(COD)]BF_4$ (7.1 mg, 0.0085 mmol, 1.0 mol %), imine (191 mg, 0.850 mmol, 1.00 equiv.) and dry CH_3CN (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (370 μL, 4.25 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (78%) was determined by the analysis of the ^1H NMR of the crude reaction mixture. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (48 mg, 1.3 mmol, 1.5 equiv) and MeOH (3 mL). The flask containing the reducing agent was brought to 0 °C and the solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature and stirred for 2 h and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **16** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 3% NH_4OH : 97% $CHCl_3$ to 6% NH_4OH : 94% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, and removing aqueous layer) afforded pure diamine **16** as a clear oil in 76% yield (202 mg, 0.646 mmol). R_f = 0.50 (1:9 $NH_4OH/CHCl_3$). ^1H NMR (C_6D_6, 500 MHz): δ 7.30 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 3.52 (ddd, J = 14.9, 6.3, 3.1 Hz, 4H), 3.46 (s, 2H), 2.50 (ddd, J = 8.6, 6.6, 4.8 Hz, 1H), 2.31 (dd, J = 11.6, 8.5 Hz, 1H), 2.26-2.17 (m, 3H), 2.07 (ddd, J = 11.2, 6.2, 3.1 Hz, 2H), 1.63 (s, 1H), 0.70 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.65, 131.36, 129.72, 120.53, 67.41, 58.66, 53.17, 51.21, 48.39, 11.44 ppm. HRMS (ESI-TOF) m/z: $[M+H^+]$ calculated for $C_{14}H_{22}BrN_2$, 313.0916; found, 313.0908.



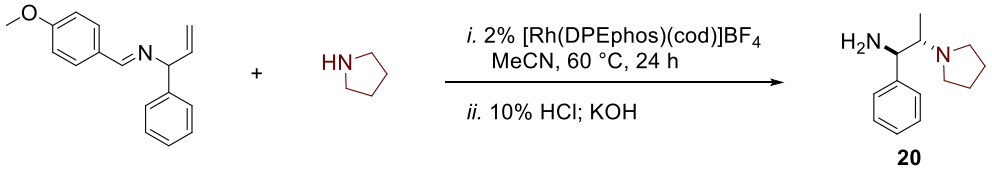
N,N-dimethyl-4-(((2-morpholinopropyl)amino)methyl)aniline, 17: [(DPEphos)Rh(COD)]BF_4 (7.2 mg, 0.0086 mmol, 1.0 mol %), imine (160 mg, 0.850 mmol, 1.00 equiv.) and dry CH_3CN (223 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added morpholine (370 µL, 4.25 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (82%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. The NMR sample was poured into the reaction vial and was rinsed with MeOH (2 mL). Meanwhile, to an oven-dried 25 mL round bottom flask was added $NaBH_4$ (48 mg, 1.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The aminoimine solution was added dropwise to the $NaBH_4$ solution. The vial was washed with MeOH (2.5 mL) and transferred to the flask. The reaction was brought to room temperature and stirred for 2 h. The resulting mixture was concentrated in vacuo. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **17** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 3% NH_4OH : 97% $CHCl_3$ to 6% NH_4OH : 94% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$ and removing aqueous layer) afforded pure diamine **17** as a clear oil in 74% yield (174 mg, 0.629 mmol). R_f = 0.33 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.34 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 3.79 (d, J = 12.9 Hz, 1H), 3.74 (d, J = 13.0 Hz, 1H), 3.53 (dtd, J = 13.9, 10.8, 5.4 Hz, 4H), 2.66-2.55 (m, 1H), 2.54-2.50 (m, 1H), 2.53 (s, 6H), 2.42 (dd, J = 11.5, 4.8 Hz, 1H), 2.29-2.21 (m, 2H), 2.15-2.07 (m, 2H), 1.80 (s, 1H), 0.75 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.70, 128.96, 128.61, 112.61, 67.45, 58.62, 53.27, 51.03, 48.32, 40.75, 11.41 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{28}N_3O$, 278.2232; found, 278.2234.



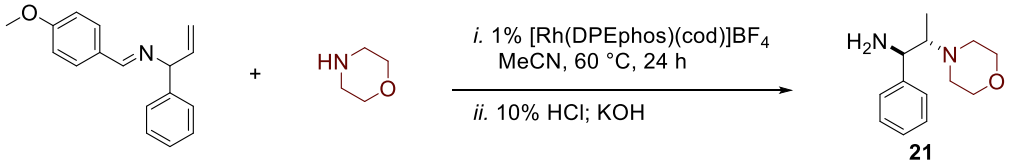
N-benzhydryl-2-morpholinopropan-1-amine, 18: $[(DPEphos)Rh(COD)]BF_4$ (42 mg, 0.050 mmol, 5.0 mol %), imine (221 mg, 1.00 mmol, 1.00 equiv.) and dry CH_3CN (350 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (216 µL, 2.50 mmol, 2.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (60%) was determined by the analysis of the ^1H NMR. Solvent was then removed under reduced pressure. The residual oil sample was rinsed into the reaction vial with THF (5 mL). Meanwhile, to an oven-dried 25 mL Schlenk flask under N_2 was added $LiAlH_4$ (76 mg, 2.0 mmol, 2.0 equiv) and THF (5 mL) and cooled to 0 °C. The solution of the aminoimine in THF was added dropwise, via syringe through septa. The reaction was brought to room temperature, stirred for 2 h, and then quenched with 1 M NaOH (5 mL). The residue was dissolved with $CHCl_3$ (20 mL) and washed with 1 M NaOH (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **18** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 1% NH_4OH : 99% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$ and removing aqueous layer) afforded pure diamine **18** as a pale yellow oil in 40% yield (137 mg, 0.600 mmol). R_f = 0.70 (1:9 MeOH/CH_2Cl_2). ^1H NMR (C_6D_6, 500 MHz): δ 7.51 (d, J = 7.0 Hz, 2H), 7.39 (d, J = 7.2 Hz, 2H), 7.16 (t, J = 7.7 Hz, 2H), 7.13 – 7.10 (m, 2H), 7.03 (dt, J = 14.8, 7.3 Hz, 2H), 4.72 (s, 1H), 3.44 (dddd, J = 19.9, 10.5, 6.9, 3.1 Hz, 4H), 2.56 (h, J = 6.7 Hz, 1H), 2.41 (d, J = 6.7 Hz, 2H), 2.17 (ddd, J = 10.3, 4.8, 2.0 Hz, 2H), 2.03 (ddd, J = 11.3, 6.1, 3.2 Hz, 2H), 1.33 (br s, 1H), 0.65 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.64, 144.33, 128.71, 128.64, 127.59 (2C, coincident peaks), 127.22, 127.12, 67.71, 67.69, 59.00, 50.87, 48.66, 11.85 ppm. HRMS (ESI-TOF) m/z: $[M+H^+]$ calculated for $C_{20}H_{27}N_2O$, 311.2123; found, 311.2123.



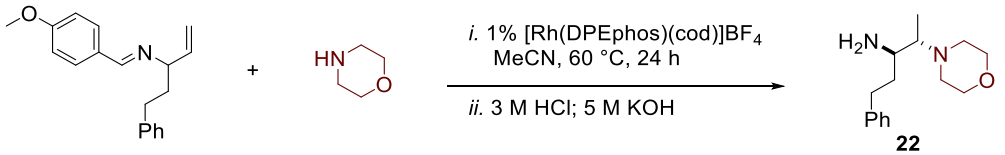
***N*-(2-morpholinopropyl)cyclohexanamine, 19**: $[(DPEphos)Rh(COD)]BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine (259 µL, 1.50 mmol, 1.00 equiv.) and dry CH_3CN (350 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (194 µL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (53%) was determined by the analysis of the ^{1}H NMR. Solvent was then removed under reduced pressure. The residual oil sample was rinsed into the reaction vial with THF (5 mL). Meanwhile, to an oven-dried 25 mL Schlenk flask was added $LiAlH_4$ (114 mg, 3.00 mmol, 2.00 equiv.) and THF (5 mL) and cooled to 0 °C. The solution of the aminoimine in THF was added dropwise, via syringe through septa. The reaction was brought to room temperature, stirred for 2 h, and then quenched with 5 mL 1 M NaOH. The residue was dissolved with $CHCl_3$ (20 mL) and washed with 1 M NaOH (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **19** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 1% saturated NH_4OH : 98% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$ and then removing aqueous layer) afforded pure diamine **19** as a pale yellow oil in 44% yield (137 mg, 0.600 mmol). R_f = 0.37 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (C_6D_6, 400 MHz): δ 3.51 (dddd, J = 13.9, 10.8, 7.0, 3.9 Hz, 4H), 2.52 (h, J = 6.6 Hz, 1H), 2.39 (d, J = 6.6 Hz, 2H), 2.33 – 2.20 (m, 2H), 2.08 (dddd, J = 9.6, 6.1, 3.6, 1.0 Hz, 2H), 1.86 – 1.69 (m, 3H), 1.63 (dq, J = 11.3, 4.2 Hz, 2H), 1.48 (dd, J = 11.9, 4.5 Hz, 1H), 1.31 – 0.95 (m, 5H), 0.73 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 171.66, 137.48, 114.00, 52.78, 39.94, 28.54, 27.82, 26.95, 26.14 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{13}H_{27}N_2O$, 227.2123; found 227.2122.



1-phenyl-2-(pyrrolidin-1-yl)propan-1-amine, 20: [(DPEphos)Rh(COD)]BF_4 (3.4 mg, 0.0040 mmol, 2.0 mol %), imine (50 mg, 0.20 mmol, 1.0 equiv.) and dry CH_3CN (53 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added pyrrolidine (17 µL, 0.20 mmol, 1.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The NMR yield (60%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with $CHCl_3$ (2 mL). The solution was concentrated in vacuo followed by the addition of 10% aqueous HCl (2 mL). The vial was capped and stirred at 60 °C for 2 h. The solution was transferred to a separatory funnel. The reaction vial was rinsed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (10 mm Hg) for 0.5 h to afford the crude diamine **20** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (4 g, MeOH : 1% NH_4OH / $CHCl_3$ = 0 : 100 to 5 : 95 as gradient afforded pure diamine **20** as a yellow oil in 50% yield (20 mg, 0.10 mmol). R_f = 0.17 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (CDCl3, 500 MHz): δ 7.37 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 4.39 (d, J = 3.1 Hz, 1H), 2.72 – 2.61 (m, 4H), 2.38 (qd, J = 6.5, 3.1 Hz, 1H), 1.85 – 1.78 (m, 4H), 1.69 (s, 2H), 0.85 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.79, 128.00, 126.80, 126.44, 66.22, 56.44, 52.32, 23.47, 11.78 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{13}H_{21}N_2$, 205.1705; found, 205.1702.

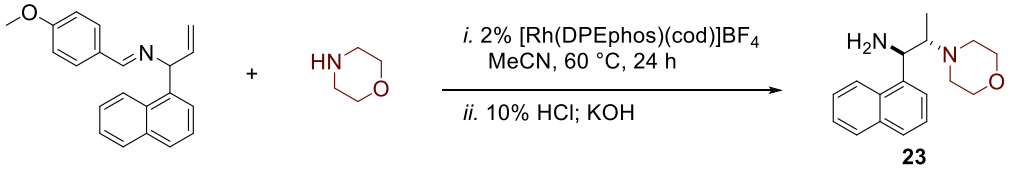


2-morpholino-1-phenylpropan-1-amine, 21: [(DPEphos)Rh(COD)]BF_4 (3.0 mg, 0.0036 mmol, 1.0 mol %), imine 12a (100 mg, 0.36 mmol, 1.0 equiv.) and dry CH_3CN (95 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (155 µL, 1.79 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (93%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with $CHCl_3$ (2 mL). The solution was then concentrated in vacuo followed by the addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **21** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (4 g, MeOH : 1% NH_4OH / $CHCl_3$ = 0 : 100 to 10 : 90 as gradient) afforded pure diamine **21** as a clear oil in 79% yield (61 mg, 0.28 mmol). R_f = 0.48 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.32 (d, J = 7.4, 2H), 7.23 (t, J = 7.6, 2H), 7.13 (t, J = 7.3, 1H), 3.94 (d, J = 4.4, 1H), 3.52 (t, J = 4.4, 4H), 2.30-2.26 (m, 1H), 2.23 (t, J = 4.5, 4H), 1.34 (s, 2H), 0.78 (d, J = 6.7, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 165.7, 162.1, 132.5, 131.4, 119.4, 118.6, 117.6, 67.5, 62.1, 60.0, 49.6, 13.3 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{13}H_{21}N_2O$, 221.1654; found, 221.1651.



4-morpholino-1-phenylpentan-3-amine, 22: [(DPEphos)Rh(COD)]BF_4 (8 mg, 0.01 mmol, 1 mol %), imine (267 µL, 1.00 mmol, 1.00 equiv.) and dry CH_3CN (300 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added

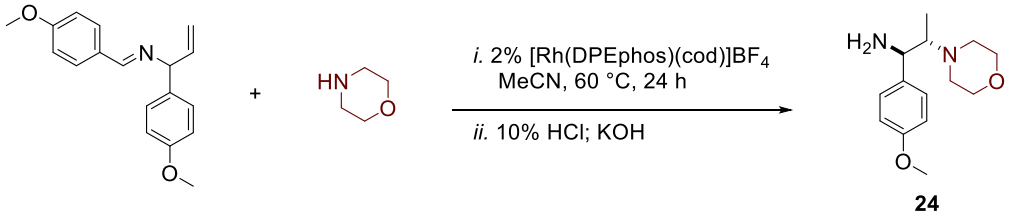
morpholine (431 µL, 5.00 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (76%) was determined by the analysis of the ^{1}H NMR. The NMR sample and remaining reaction mixture were rinsed into a separate 20 mL scintillation vial with $CHCl_3$ (3 mL) and the solvent was reduced under reduced pressure. 3 M HCl (5 mL) was then added to the scintillation and the diphasic solution was vigorously stirred for 18 hours. The organic layer was discarded and the aqueous layer was basified with 5 M NaOH until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (75 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude diamine **22** as yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 2% MeOH : 2% NH_4OH: 96% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **22** as a pale yellow oil in 73% yield (119 mg, 0.731 mmol). R_f = 0.40 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.19 – 7.14 (m, 3H), 7.09 – 7.03 (m, 2H), 3.57 – 3.46 (m, 4H), 2.72 (ddd, J = 13.6, 9.8, 5.2 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.14 (tq, J = 10.8, 6.1, 4.9 Hz, 4H), 1.86 (p, J = 6.5 Hz, 1H), 1.79 (dddd, J = 13.3, 10.1, 7.0, 3.3 Hz, 1H), 1.40 (dddd, J = 13.8, 9.7, 8.7, 5.2 Hz, 1H), 0.72 (d, J = 6.6 Hz, 5H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 142.65, 128.60, 128.59, 126.00, 67.70, 64.20, 51.77, 50.60, 37.04, 33.17, 9.73 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1963.



23

2-morpholino-1-(naphthalen-1-yl)propan-1-amine, **23**: [(DPEphos)Rh(COD)]BF_4 (3.4 mg, 0.0040 mmol, 2.0 mol %), imine (60 mg, 0.20 mmol, 1.0 equiv.) and dry CH3CN (53 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added morpholine, (88 µL, 1.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The NMR yield (78%) was determined by the analysis of the ^{1}H NMR of the

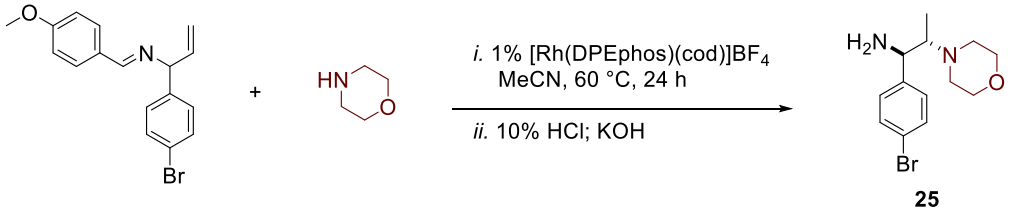
crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with $CHCl_3$ (2 mL). The solution was then concentrated in vacuo followed by the addition of 10% aqueous HCl (2 mL). The vial was capped and stirred at 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was rinsed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (10 mm Hg) for 0.5 h to afford the pure diamine **23** as an off-white solid in 78% yield (42 mg, 0.16 mmol). m.p. 103–105 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ 8.06 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.39 (ddd, J = 8.7, 7.0, 1.7 Hz, 2H), 7.30 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 4.93 (d, J = 3.5 Hz, 1H), 3.54 (q, J = 4.2 Hz, 4H), 2.60 (qd, J = 6.6, 3.5 Hz, 1H), 2.34 (t, J = 4.5 Hz, 4H), 1.17 (s, 2H), 0.77 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.21, 135.12, 132.33, 130.07, 128.11, 126.40, 126.35, 126.03, 125.73, 124.01, 68.17, 64.20, 51.95, 51.87, 10.84 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{17}H_{23}N_2O$, 271.1810; found, 270.1803.



24

1-(4-methoxyphenyl)-2-morpholinopropan-1-amine, **24**: [(DPEphos)Rh(COD)]BF_4 (4.5 mg, 0.0054 mmol, 2.0 mol %), imine 12d (77 mg, 0.27 mmol, 1.0 equiv.) and dry CH_3CN (72 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (120 µL, 1.4 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (92%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with $CHCl_3$ (2 mL). The solution was then concentrated in vacuo followed by the

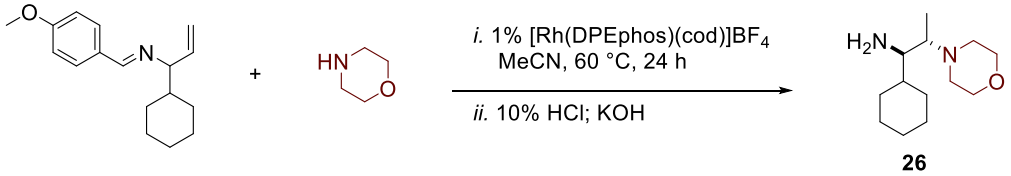
addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **24** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (24 g, MeOH : 1% NH_4OH / $CHCl_3$ = 0 : 100 to 10 : 90 as gradient) afforded pure diamine **24** as a clear oil in 80% yield (54 mg, 0.22 mmol). R_f = 0.48 (1:9 $NH_4OH/CHCl_3$). ^1H NMR (C_6D_6, 500 MHz): δ 7.26 (d, J = 8.3, 2H), 6.88 (d, J = 8.7, 2H), 3.94 (d, J = 4.4, 1H), 3.54 (t, J = 4.5, 4H), 3.37 (s, 3H), 2.30-2.25 (m, 5H), 1.19 (s, 2H), 0.83 (d, J = 6.7, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 128.34, 159.03, 137.3, 113.8, 67.6, 66.0, 55.4, 54.8, 51.3, 10.1 ppm. HRMS (ESI-TOF) m/z: [$M+H^+$] calculated for $C_{14}H_{23}N_2O_2$, 251.1760; found, 251.1759.



25

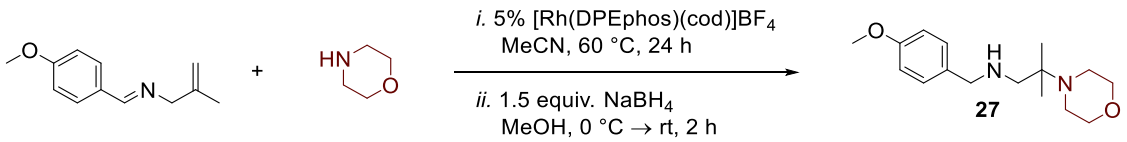
1-(4-bromophenyl)-2-morpholinopropan-1-amine, 25: [(DPEphos)Rh(COD)]BF_4 (2.5 mg, 0.0030 mmol, 1.0 mol %), imine (100 mg, 0.30 mmol, 1.0 equiv.) and dry CH_3CN (80 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added morpholine (79 µL, 0.90 mmol, 3.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The NMR yield (74%) was determined by the analysis of the ^1H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with $CHCl_3$ (2 mL). The solution was then concentrated in vacuo followed by the addition of 10% aqueous HCl (3 mL). The vial was then capped and stirred at 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was rinsed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3)

and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo followed by drying under high vacuum (10 mm Hg) for 0.5 h to afford the pure diamine **25** as an off white solid in 69% yield (62 mg, 0.21 mmol). m.p. 63–65 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.33 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.3 Hz, 2H), 3.69 (d, J = 4.6 Hz, 1H), 3.48 (t, J = 5.0 Hz, 4H), 2.15 (td, J = 4.2, 1.9 Hz, 4H), 2.09 (qd, J = 6.7, 4.6 Hz, 1H), 0.95 (s, 2H), 0.67 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.96, 131.86, 129.75, 121.09, 68.03, 66.20, 56.00, 51.64, 10.53 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calcd for $C_{13}H_{20}N_2OBr$, 299.0759; found, 299.0761.

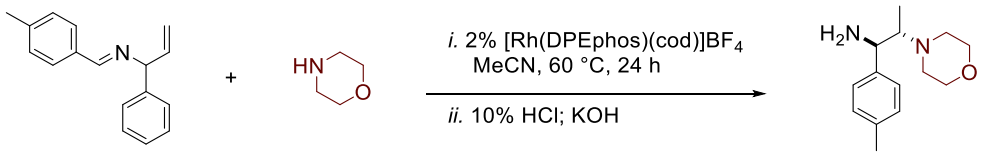


26

1-cyclohexyl-2-morpholinopropan-1-amine, 26: [(DPEphos)Rh(COD)]BF_4 (8 mg, 0.01 mmol, 1 mol %), imine (257 mg, 1.00 mmol, 1.00 equiv.) and dry CH_3CN (300 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (604 µL, 7.00 mmol, 7.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of diphenylmethane as an internal standard. The reaction mixture was further dissolved in C_6D_6 (0.5 mL). The crude yield (78%) was determined by the analysis of the ^{1}H NMR. Subjection of the crude aminoimine **26** to silica gel chromatography (125 mL silica, 1% MeOH : 1% NH_4OH : 98% $CHCl_3$ to 2% MeOH : 2% NH_4OH : 96% $CHCl_3$ gradient v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded 1,2-diamine **26** as a pale yellow oil in 58% yield (141 mg, 1.08 mmol). Rf = 0.53 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (C_6D_6, 500 MHz): δ 3.67 – 3.43 (m, 4H), 2.35 (t, J = 5.8 Hz, 1H), 2.20 (tq, J = 11.4, 6.4, 5.4 Hz, 4H), 2.07 (p, J = 6.5 Hz, 1H), 1.69 (td, J = 25.1, 23.3, 13.1 Hz, 4H), 1.42 (d, J = 9.0 Hz, 2H), 1.29 – 1.05 (m, 3H), 1.01 – 0.84 (m, 2H), 0.82 (d, J = 6.6 Hz, 5H) ppm. ^{13}C NMR (C6D6, 125 MHz): δ 67.49, 61.10, 56.73, 50.30, 40.43, 30.27, 28.24, 27.03, 26.86, 26.70, 9.60 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{13}H_{27}N_2O$, 227.2123; found, 227.2121.



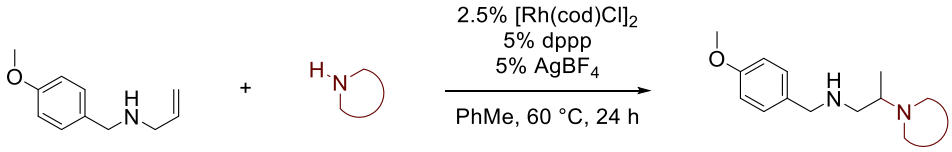
(E)-1-(4-methoxyphenyl)-N-(2-methyl-2-morpholinopropyl)methanimine, **27**: [(DPEphos)Rh(COD)]BF_4 (12 mg, 0.015 mmol, 5.0 mol %), imine (54.5 mg, 0.288 mmol, 1.00 equiv.) and dry CH_3CN (77 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (126 μL, 1.46 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (78%) was determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with MeOH (0.5 mL). Meanwhile, to an oven-dried 10 mL round bottom flask was added $NaBH_4$ (17 mg, 0.44 mmol, 1.5 equiv.) and MeOH (0.5 mL). The flask containing the reducing agent was brought to 0 °C and the solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (0.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated in vacuo. The residue was dissolved with $CHCl_3$ (10 mL) and was washed with saturated $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **27** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 2% NH_4OH : 98% $CHCl_3$ to 2% NH_4OH : 2% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **27** as a clear oil in 58% yield (46 mg, 0.17 mmol). R_f = 0.53 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 7.25 (d, J = 8.6, 2H), 6.82 (d, J = 8.6, 2H), 3.67 (s, 2H), 3.54 (t, J = 4.6, 4H), 3.33 (s, 3H), 2.35 (s, 2H), 2.19 (t, J = 4.6, 4H), 0.90 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 133.4, 129.4, 113.9, 67.8, 56.7, 56.0, 54.6, 53.7, 45.9, 21.7 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{27}N_2O_2$, 279.2073; found, 279.2075.



2-morpholino-1-(p-tolyl)propan-1-amine: [(DPEphos)Rh(COD)]BF_4 (5.5 mg, 0.0066 mmol, 2.0 mol %), imine (82 mg, 0.33 mmol, 1.0 equiv.) and dry CH_3CN (87 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (140 µL, 1.6 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature followed by the addition of tetramethylsilane as an internal standard. The reaction mixture was further dissolved in $CDCl_3$ (0.5 mL). The NMR yield (90%) was then determined by the analysis of the ^{1}H NMR of the crude reaction mixture. After the analysis, the NMR sample was poured into the reaction vial and was rinsed with $CHCl_3$ (2 mL). The solution was then concentrated in vacuo followed by the addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated in vacuo followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine as yellow oil. Purification of the crude diamine by automated silica gel chromatography (4 g, MeOH : 1% NH_4OH / $CHCl_3$ = 0 : 100 to 18 : 82 as gradient) afforded pure diamine as a clear oil in 67% yield (52 mg, 0.22 mmol). R_f = 0.40 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500MHz): δ 7.27 (d, J = 8.0, 2H), 7.08 (d, J = 7.8, 2H), 3.96 (d, J = 4.3, 1H), 3.54 (dd, J = 5.0, 2.9, 4H), 2.30 (qd, J = 6.7, 4.4, 1H), 2.25 (t, J = 4.6, 4H), 2.19 (s, 3H), 1.22 (s, 2H), 0.82 (d, J = 6.7, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 142.3, 136.0, 129.0, 127.4, 67.6, 66.0, 55.6, 51.3, 21.1, 10.1 ppm. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1812

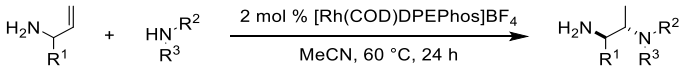
2.8.2 Hydroamination of allylic amines

General Procedure A:



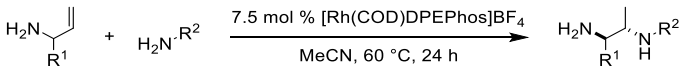
To a 4 mL vial equipped with stir bar was added $[Rh(cod)Cl]_2$ (6.16 mg, 0.0125 mmol, 2.5%), dppp (10.3 mg, 0.25 mmol, 5%), and $AgBF_4$ (4.87 mg, 0.25 mmol, 5%). Toluene (143 μL, 3.5 M) was then added followed by the secondary allylic amine substrate (89 mg, 0.5 mmol, 1 equiv.) and secondary amine nucleophile (1.0-2.5 mmol, 2-5 equiv.). The vial was sealed with a Teflon cap, removed from the nitrogen filled glove box, and heated to 60 °C for 24 h. The reaction was then cooled to room temperature, volatiles were removed *en vacuo*, and the crude was purified by column chromatography using 100 mL silica, a 1" diameter column, and a mobile phase. The mobile phase was prepared by extracting 40 mL of saturated ammonium hydroxide with 1 L $CHCl_3$ and removing the aqueous layer. The polarity of the chloroform/ammonia solution was then increased by adding up to 8% MeOH (v/v) to obtain the purified product.

General Primary Allyl Amine Hydroamination Procedure B:

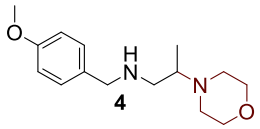


$[(DPEphos)Rh(COD)]BF_4$ (8.4 mg, 0.01 mmol, 2.0 mol %), allylamine (0.50 mmol, 1.0 equiv.), amine nucleophile (1.5 mmol, 3.0 equiv.),and dry CH_3CN (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. The resulting solution was allowed to stir for 2 h at 60 °C. The reaction vial was cooled to room temperature and was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine as yellow oil. The diamine was further dissolved in $CHCl_3$ (10 mL). 6 M HCl was then added to the flask until a pH ~1 was obtained. The organic layer was then discarded and the aqueous layer was washed with $CHCl_3$ (20 mL × 3). The final aqueous layer was basified with 3 M NaOH until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (30 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford pure diamine.

General Primary Allyl Amine Hydroamination Procedure C:



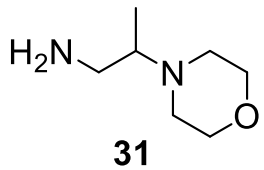
[(DPEphos)Rh(COD)]BF_4 (25 mg, 0.030 mmol, 7.5 mol %), amine **9a** (54 mg, 0.40 mmol, 1.0 equiv.), and dry CH_3CN (100 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added primary amine nucleophile (2.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature. Purification of the crude diamine by silica gel chromatography (10 g silica, 100% $CHCl_3$ to 3% NH_4OH : 1% MeOH: 96% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded the pure diamine after drying under high vacuum (0.05 mm Hg) at 60 °C for 1 h.



4

***N*-(4-methoxybenzyl)-2-morpholinopropan-1-amine, 4**: The compound was prepared according to general procedure A using morpholine (216 μL, 2.5 mmol, 5 equiv.) as the nucleophilic amine partner. The pale yellow oil (98.7 mg, 0.37 mmol) was obtained in 75% yield.

R_f = 0.56 (1:9 $NH_4OH/CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.70 (d, *J* = 13.1 Hz, 1H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.52 (dddd, *J* = 19.9, 10.7, 6.1, 3.0 Hz, 4H), 3.34 (s, 3H), 2.58 (dqd, *J* = 8.7, 6.6, 4.8 Hz, 1H), 2.45 (dd, *J* = 11.6, 8.4 Hz, 1H), 2.36 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.28 – 2.16 (m, 3H), 2.10 (ddd, *J* = 11.2, 6.1, 3.1 Hz, 2H), 0.73 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 159.25, 133.54, 129.55, 114.09, 67.56, 59.02, 54.83, 53.68, 51.68, 48.90, 11.82 ppm. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1913.

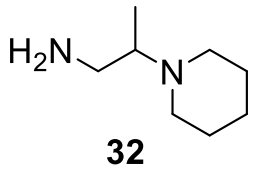


31

2-morpholinopropan-1-amine, 31: [(DPEphos)Rh(COD)]BF_4 (14.2 mg, 0.017 mmol, 2.0 mol %), amine **7** (64 μL, 0.85 mmol, 1.00 equiv.) and dry CH_3CN (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (446 μL, 5.1 mmol, 6.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After

24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (15 mm Hg) for 10 min to afford crude **31** as a yellow oil. Purification of the crude diamine by silica gel chromatography (3 X 9 cm^2, NH_4OH : $CHCl_3$ (1:20 then 1:15 then 1:6 followed by 1:3) v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:20 NH_4OH : $CHCl_3$ as eluent) afforded pure diamine **31** as a pale yellow oil in 20% yield (25 mg, 0.17 mmol) after drying under high vacuum (15 mm Hg) for 10 min. A second column of the remained residue (came down the column as mixture of diamine, morpholine and some unknown impurities from the first column) with same conditions gave another batch of diamine **31** in 25% yield (31 mg, 0.21 mmol). The remaining mixture contained diamine **31** and morpholine which was kept under high vacuum (15 mm Hg) for 10 min to afford the third batch of diamine **31** in 27% yield (33 mg, 0.23 mmol). A total of 72% yield (89 mg, 0.61 mmol) of diamine **31** was obtained. The time slot for keeping the diamine **31** under the vacuum at 15 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.

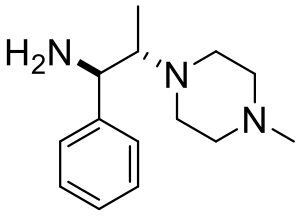
R_f = 0.34 (1:2 $NH_4OH/CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 3.73 – 3.59 (m, 4H), 2.67 – 2.59 (m, 1H), 2.59 – 2.42 (m, 4H), 2.42 – 2.34 (m, 2H), 1.52 (s, 2H), 0.91 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 67.39, 61.62, 48.61, 44.22, 11.40 ppm. HRMS (ESI-TOF) *m/z*: $[M+H^+]$ calculated for $C_7H_{17}N_2O$, 145.1341; found, 145.1337.



32

2-(piperidin-1)propan-1-amine, 32: $[(DPEphos)Rh(COD)]BF_4$ (14.2 mg, 0.017 mmol, 2.0 mol %), amine **7** (64 μL, 0.85 mmol, 1.00 equiv.) and dry CH_3CN (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added piperidine (504 μL, 5.1 mmol, 6.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (25 mm Hg) for 10 min to afford crude **32** as a yellow oil. Purification of the crude diamine by silica gel chromatography (3 X 9 cm^2, NH_4OH : $CHCl_3$ (1:20 then 1:15 then 1:6 followed by 1:3) v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:20 NH_4OH : $CHCl_3$ as eluent) afforded

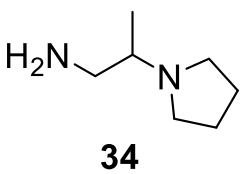
pure diamine **32** as a pale yellow oil in 23% yield (28 mg, 0.20 mmol) after drying under high vacuum (15 mm Hg) for 10 min. A second column of the remained residue (came down the column as mixture of diamine, piperidine and some unknown impurities from the first column) with same conditions gave another batch of diamine **32** in 22% yield (27 mg, 0.19 mmol). The remaining mixture contained diamine **32** and piperidine which was kept under high vacuum (25 mm Hg) for 10 min to afford the third batch of diamine **32** in 15% yield (18 mg, 0.13 mmol). A total of 60% yield (73 mg, 0.52 mmol) of diamine **32** was obtained. The time slot for keeping the diamine **8b** under the vacuum at 25 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.



33

2-morpholino-1-phenylpropan-1-amine, 33: The general primary allyl amine hydroamination procedure B was followed using allyl amine (55 mg, 0.40 mmol, 1.00 equiv.) and *N*-methylpiperazine, **2a** (120 μL, 1.2 mmol, 3.0 equiv., freshly distilled) and was run for 4 hours. Diamine **33** was isolated as a pale yellow oil in 65% yield (59 mg, 0.25 mmol).

^{1}H NMR ($CDCl_3$, 500 MHz) ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.33 (d, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 4.01 (d, *J* = 4.4 Hz, 1H), 2.50 – 2.38 (m, 5H), 2.24 (s, 4H), 2.11 (s, 3H), 1.32 (s, 2H), 0.85 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz) δ ^{13}C NMR (126 MHz, Benzene) δ 145.60, 128.19, 127.47, 126.69, 65.53, 56.40, 56.14, 50.56, 46.31, 10.49.

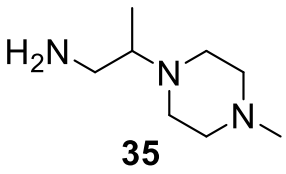


34

2-(pyrrolidin-1-yl)propan-1-amine, 34: [(DPEphos)Rh(COD)]BF_4 (14.2 mg, 0.017 mmol, 2.0 mol %), allyl amine (64 μL, 0.85 mmol, 1.00 equiv.) and dry CH_3CN (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added pyrrolidine (284μL, 3.4 mmol, 4.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (15 mm Hg) for 10 min to afford crude **34** as a yellow oil. Purification

of the crude diamine by silica gel chromatography (3 X 9 cm^2, NH_4OH : $CHCl_3$ (1:10 followed by 1:8) v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:10 NH_4OH : $CHCl_3$ as eluent) afforded pure diamine **8e** as a pale yellow oil in 37% yield (40 mg, 0.31 mmol) after drying under high vacuum (15 mm Hg) for 10 min. The remaining mixture contained diamine **34** and pyrrolidine which was kept under high vacuum (15 mm Hg) for 10 min to afford the second batch of diamine **34** in 8% yield (9 mg, 0.07 mmol). A total of 45% yield (49 mg, 0.38 mmol) of diamine **34** was obtained. The time slot for keeping the diamine **34** under the vacuum at 15 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.

R_f = 0.22 (1:2 $NH_4OH/CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 2.73 (d, *J* = 5.1 Hz, 2H), 2.56 (td, *J* = 5.4, 4.1, 2.6 Hz, 4H), 2.31 (dtd, *J* = 11.5, 6.4, 5.0 Hz, 1H), 1.82 – 1.70 (m, 4H), 1.64 (s, 2H), 1.09 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 60.86, 51.01, 46.49, 23.40, 15.57 ppm. HRMS (ESI-TOF) *m/z*: [$M+H^+$] calculated for $C_8H_{17}N_2$, 129.1392; found, 129.1388.



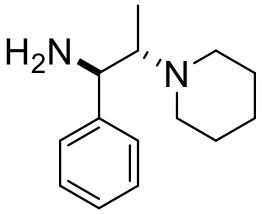
35

2-(4-methylpiperazin-1-yl)propan-1-amine, 35: [(DPEphos)Rh(COD)]BF_4 (14.2 mg, 0.017 mmol, 2.0 mol %), amine **7** (64 μL, 0.85 mmol, 1.00 equiv.) and dry CH_3CN (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added *N*-methylpiperazine, (377μL, 3.4 mmol, 4.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (8 mm Hg) for 10 min to afford crude **35** as a yellow oil. Purification of the crude diamine by silica gel chromatography (3 X 9 cm^2, NH_4OH : $CHCl_3$ (1:20 then 1:15 then 1:6 followed by 1:3) v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:20 NH_4OH : $CHCl_3$ as eluent) afforded pure diamine **8'c** as a pale yellow oil in 35% yield (48 mg, 0.30 mmol) after drying under high vacuum (8 mm Hg) for 10 min. A second column of the remained residue (came down the column as mixture of diamine, *N*-methylpiperazine and some unknown impurities from the first column) with same

conditions gave another batch of diamine **35** in 22% yield (29 mg, 0.19 mmol). The remaining mixture contained diamine **35** and *N*-methylpiperazine which was kept under high vacuum (8 mm Hg) for 10 min to afford the third batch of diamine **35** in 6% yield (8 mg, 0.05 mmol). A total of 63% yield (85 mg, 0.54 mmol) of diamine **35** was obtained. The time slot for keeping the diamine **35** under the vacuum at 8 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.

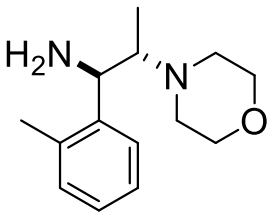
R_f = 0.22 (1:2 $NH_4OH/CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 2.71 – 2.48 (m, 5H), 2.51 – 2.30 (m, 6H), 2.26 (s, 5H), 0.92 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 60.91, 55.57, 55.46, 46.04, 44.23, 29.66, 11.38 ppm. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_8H_{20}N_3$, 158.1657; found, 158.1650.

HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1806.



37

2-morpholino-1-phenylpropan-1-amine, 37: The general primary allyl amine hydroamination procedure B was followed using allyl amine (53 mg, 0.40 mmol, 1.00 equiv.) and piperidine (37 μL, 0.44 mmol, 1.1 equiv., freshly distilled) and was run for 8 hours. Diamine **37** was isolated as a pale yellow oil in 57% yield (48 mg, 0.22 mmol).



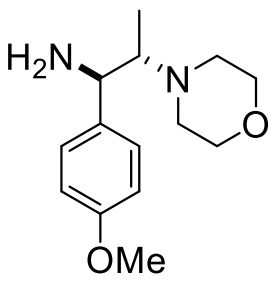
38

2-morpholino-1-(*o*-tolyl)propan-1-amine, 38: The general primary allyl amine hydroamination procedure B was followed using allyl amine (113 mg, 0.85 mmol, 1.00 equiv.) and morpholine (223 μL, 1.2 mmol, 3.0 equiv., freshly distilled) and was run for 24 hours. Diamine **38** was isolated as a pale yellow oil in 75% yield (149 mg, 0.64 mmol).

^1H NMR (C_6D_6, 500MHz) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.10 (td, *J* = 7.4, 1.4 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 4.26 (d, *J* = 3.8 Hz, 1H), 3.54 (t, *J* = 4.6 Hz, 4H), 2.27 (dq, *J* = 12.2, 3.8, 2.9 Hz, 5H), 2.14 (s, 3H), 1.08 (s, 2H), 0.85 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (C_6D_6, 125 MHz): δ 142.94, 134.98, 130.51, 127.75, 126.67, 126.13, 67.60, 63.14, 51.79, 51.29, 19.47, 10.06 ppm.

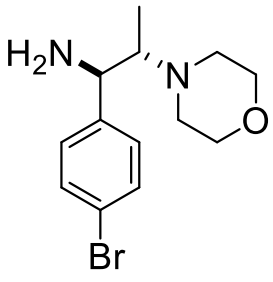
HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1806.



39

1-(4-methoxyphenyl)-2-morpholinopropan-1-amine, 39: The general primary allyl amine hydroamination procedure B was followed using allyl amine (82 mg, 0.50 mmol, 1.00 equiv.) and morpholine (175 μL, 2.0 mmol, 4.0 equiv., freshly distilled) and was run for 24 hours. Diamine **39**was isolated as an off white solid in 80% yield (100 mg, 0.40 mmol).

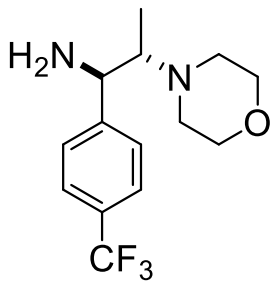
m.p. 63–65 °C. ^{1}H NMR (C_6D_6, 500 MHz) δ 7.27 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 3.95 (d, *J* = 4.1 Hz, 1H), 3.55 (dd, *J* = 5.6, 3.8 Hz, 4H), 3.36 (s, 3H), 2.35 – 2.20 (m, 5H), 1.37 (s, 2H), 0.84 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz) δ 159.04, 137.03, 128.37, 113.78, 67.58, 65.96, 55.34, 54.82, 51.29, 10.16 ppm. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O_2$, 251.1760; found, 251.1754.



40

1-(4-bromophenyl)-2-morpholinopropan-1-amine, 40: The general primary allyl amine hydroamination procedure B was followed using allyl amine (106 mg, 0.50 mmol, 1.00 equiv.) and morpholine (87 μL, 1.0 mmol, 2.0 equiv., freshly distilled). Diamine **40** was isolated as an off white solid in 80% yield (120 mg, 0.40 mmol).

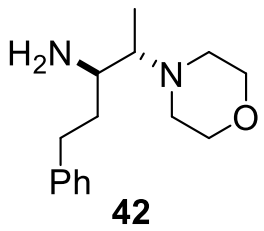
m.p. 64–66 °C. ^{1}H NMR (C_6D_6, 500 MHz) δ 7.35 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.70 (d, *J* = 4.6 Hz, 1H), 3.57 – 3.41 (m, 4H), 2.16 (dd, *J* = 6.0, 3.6 Hz, 4H), 2.09 (qd, *J* = 6.7, 4.6 Hz, 1H), 0.96 (s, 2H), 0.68 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 500 MHz) δ 144.33, 131.30, 129.19, 120.55, 67.46, 65.60, 55.34, 51.08, 9.97 ppm. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{13}H_{20}N_2OBr$, 299.0759; found, 299.0755.



41

1-(4-(trifluoromethyl)phenyl)-2-morpholinopropan-1-amine, 41: The general primary allyl amine hydroamination procedure B was followed using allyl amine (64 mg, 0.32 mmol, 1.00 equiv.) and morpholine (56 μL, 0.64 mmol, 2.0 equiv., freshly distilled). Diamine **41** was isolated as a clear oil in 91% yield (84 mg, 0.29 mmol).

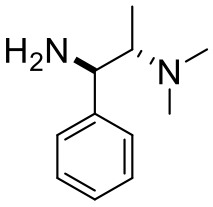
^{1}H NMR (C_6D_6, 500 MHz): δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 3.75 (d, *J* = 4.7 Hz, 1H), 3.48 (t, *J* = 4.6 Hz, 4H), 2.21 – 2.08 (m, 5H), 1.10 – 0.92 (m, 2H), 0.66 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz) δ 149.63, 128.95 (q, $^2J_{CF}$ = 32.1 Hz), 125.25 (d, $^1J_{CF}$ = 271.7 Hz), 125.07 (q, $^3J_{CF}$ = 3.8 Hz), 67.42, 65.59, 55.65, 51.00, 9.91 ppm. ^{19}F NMR (C_6D_6, 470 MHz) δ –62.23. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{14}H_{20}N_2OF_3$, 289.1528; found, 289.1524.



42

4-morpholino-1-phenylpentan-3-amine, 42: The general primary allyl amine hydroamination procedure B was followed using allyl amine (81 mg, 0.50 mmol, 1.00 equiv.) and morpholine (175 μL, 2.0 mmol, 4.0 equiv., freshly distilled) and was run for 24 hours. Diamine **42** was isolated as a clear oil in 75% yield (93 mg, 0.38 mmol).

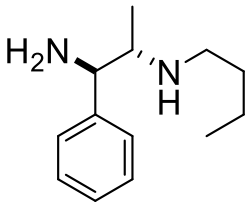
^{1}H NMR (C_6D_6, 500 MHz) δ 7.22 – 7.17 (m, 4H), 7.12 – 7.07 (m, 1H), 3.60 – 3.48 (m, 4H), 2.75 (ddd, *J* = 13.6, 9.8, 5.1 Hz, 1H), 2.60 – 2.51 (m, 2H), 2.16 (dtdd, *J* = 15.4, 11.2, 7.2, 3.5 Hz, 4H), 1.89 (dt, *J* = 13.1, 6.5 Hz, 1H), 1.82 (dddd, *J* = 13.3, 10.2, 7.1, 3.3 Hz, 1H), 1.42 (dddd, *J* = 13.7, 9.5, 8.8, 5.1 Hz, 1H), 0.75 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz) δ 143.14, 128.83, 128.69, 126.08, 67.58, 64.51, 51.79, 50.52, 37.27, 33.14, 9.40 ppm. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1969.



43

N^2,N^2-dimethyl-1-phenylpropane-1,2-diamine, 43: [(DPEphos)Rh(COD)]BF_4 (8.5 mg, 0.010 mmol, 5.0 mol %) and allyl amine (27 mg, 0.20 mmol, 1.0 equiv.) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added *N*,*N*-dimethylamine (1.0 mL, 1.4M in THF, 1.4 mmol, 7.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature. The reaction mixture was then concentrated *in vacuo* to afford the crude diamine **43** as yellow oil. Purification of the crude diamine by silica gel chromatography (10 g silica, 100% $CHCl_3$ to 3% NH_4OH : 1% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **43** as a pale yellow oil in 80% yield (30 mg, 0.17 mmol).

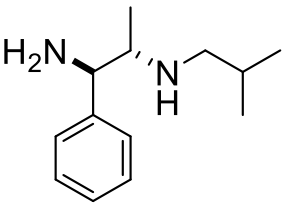
R_f = 0.12 (1:9 NH_4OH /CHCl3). ^1H NMR (C_6D_6, 500 MHz) δ 7.34 (d, J = 7.7 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 4.00 (d, J = 4.8 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.07 (s, 6H), 1.47 (s, 2H), 0.86 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (126 MHz, Benzene) δ 145.55, 128.27, 127.45, 126.73, 66.32, 56.81, 42.90, 10.23. HRMS (ESI-TOF) m/z: [M+H+] calculated for C11H19N2, 179.1548; found, 179.1546.



44

N^2-butyl-1-phenylpropane-1,2-diamine, 44: The general primary allyl amine hydroamination procedure C was followed using allyl amine (54 mg, 0.40 mmol, 1.0 equiv.) and *N*-butylamine (146 mg, 2.0 mmol, 5.0 equiv.). Diamine **44** was isolated as a pale yellow oil in 67% yield (57 mg, 0.28 mmol).

R_f = 0.20 (1:9 NH_4OH /CHCl3). ^1H NMR (C_6D_6, 500 MHz) δ 7.34 (d, J = 7.6 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.93 (d, J = 4.1 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.51 (dt, J = 11.2, 7.0 Hz, 1H), 2.44 (dt, J = 11.2, 7.0 Hz, 1H), 1.44 – 1.30 (m, 8H), 1.27 – 1.21 (m, 2H), 0.88 – 0.83 (m, 6H) ppm. ^{13}C NMR (126 MHz, Benzene) δ 144.90, 128.31, 127.63, 126.91, 59.51, 58.57, 47.59, 33.09, 20.87, 15.34, 14.30. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{13}H_{23}N_2$, 207.1861; found, 207.1871.

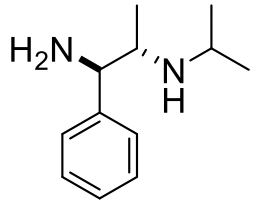


45

N^2-isobutyl-1-phenylpropane-1,2-diamine, 45: The general primary allyl amine hydroamination procedure C was followed using allyl amine (54 mg, 0.40 mmol, 1.0 equiv.) and *N*-isobutylamine, (146 mg, 2.0 mmol, 5.0 equiv.). Diamine **45** was isolated as a pale yellow oil in 58% yield (49 mg, 0.24 mmol).

R_f = 0.20 (1:9 NH_4OH /CHCl3). ^1H NMR (C_6D_6, 500 MHz) δ 7.34 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.86 (d, J = 4.3 Hz, 1H), 2.73 – 2.67 (m, 1H), 2.34 (dd, J = 11.2, 6.5 Hz, 1H), 2.25 (dd, J = 11.2, 6.8 Hz, 1H), 1.51 (dp, J = 13.3, 6.6 Hz, 1H), 1.10 (s, 3H), 0.88 – 0.82 (m, 9H) ppm. ^{13}C NMR (126 MHz, Benzene) δ 144.89, 128.31, 127.61, 126.92, 59.55,

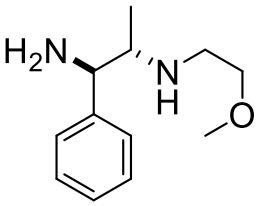
58.57, 55.98, 29.23, 20.91, 15.44. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{13}H_{23}N_2$, 207.1861; found, 207.1871.



46

N^2-isopropyl-1-phenylpropane-1,2-diamine, 46: The general primary allyl amine hydroamination procedure C was followed using allyl amine (54 mg, 0.40 mmol, 1.0 equiv.), and *N*-isopropylamine (120 mg, 2.0 mmol, 5.0 equiv.). Diamine **46** was isolated as a pale yellow oil in 60% yield (47 mg, 0.24 mmol).

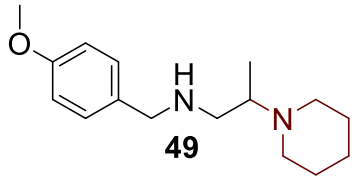
R_f = 0.13 (1:9 NH_4OH /CHCl3). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.31 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.81 (d, J = 4.0 Hz, 1H), 2.85 (qd, J = 6.4, 4.2 Hz, 1H), 2.71 (hept, J = 6.2 Hz, 1H), 0.98 (s, 3H), 0.92 (d, J = 6.2 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, Benzene) δ 144.00, 128.37, 127.56, 127.03, 58.37, 55.93, 46.22, 23.21, 22.69, 14.84. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{12}H_{21}N_2$, 193.1705; found, 193.1710.



47

N^2-(2-methoxyethyl)-1-phenylpropane-1,2-diamine, 47: The general primary allyl amine hydroamination procedure C was followed using allyl amine (54 mg, 0.40 mmol, 1.0 equiv.) and 2-methoxyethylamine (150 mg, 2.0 mmol, 5.0 equiv.). Diamine **47** was isolated as a pale yellow oil in 70% yield (59 mg, 0.28 mmol).

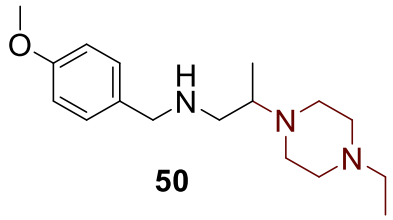
R_f = 0.13 (1:9 NH_4OH /CHCl3). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.33 (d, J = 7.2 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 3.87 (d, J = 4.1 Hz, 1H), 3.25 (t, J = 5.3 Hz, 2H), 3.06 (s, 3H), 2.77 – 2.66 (m, 2H), 2.61 (dt, J = 12.0, 5.2 Hz, 1H), 1.27 (s, 3H), 0.85 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, Benzene) δ 144.75, 128.28, 127.61, 126.87, 72.66, 59.39, 58.47, 58.45, 47.49, 14.95. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{12}H_{21}N_2O$, 209.1654; found, 209.1660.



49

***N*-(4-methoxybenzyl)-2-(piperidin-1-yl)propan-1-amine, 49**: The compound was prepared according to general procedure A using piperidine (148 μL, 1.5 mmol, 3 equiv.) as the nucleophilic amine partner. The pale yellow oil (91.8 mg, 0.35 mmol) was obtained in 70.% yield.

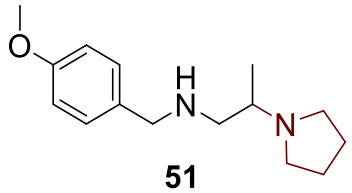
R_f = 0.60 (1:9 $NH_4OH/CHCl_3$). ^1H NMR (C_6D_6, 500 MHz) δ 7.32 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.72 (d, *J* = 13.1 Hz, 1H), 3.33 (s, 3H), 2.82 – 2.72 (m, 1H), 2.60 – 2.53 (m, 1H), 2.43 (ddd, *J* = 11.5, 4.9, 1.0 Hz, 1H), 2.38 (ddd, *J* = 10.9, 7.2, 3.4 Hz, 2H), 2.24 – 2.12 (m, 2H), 1.77 (brs, 1H), 1.53 – 1.36 (m, 4H), 1.30 (p, *J* = 6.0 Hz, 2H), 0.78 (d, *J* = 6.6 Hz, 3H) ppm.^{13}C NMR (C_6D_6, 125 MHz) δ 159.17, 133.84, 129.53, 114.05, 59.37, 54.82, 53.80, 52.30, 49.44, 27.08, 25.46, 11.42 ppm. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{16}H_{27}N_2O$, 263.2123; found, 263.2119.



50

2-(4-ethylpiperazin-1-yl)-*N*-(4-methoxybenzyl)propan-1-amine, 50: The compound was prepared according to general procedure A using 1-ethylpiperazine (127 μL, 1.0 mmol, 2 equiv.) as the nucleophilic amine partner. The pale yellow oil (56.2 mg, 0.19 mmol) was obtained in 39% yield.

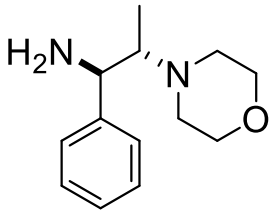
R_f = 0.28 (1:8 $NH_4OH/CHCl_3$). ^1H NMR (C_6D_6, 500 MHz): δ 7.32 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.33 (s, 3H), 2.78 (dqd, *J* = 8.9, 6.6, 4.8 Hz, 1H), 2.60 – 2.41 (m, 5H), 2.41 – 2.28 (m, 6H), 2.24 (qd, *J* = 7.2, 0.9 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ 159.26, 133.41, 129.65, 114.08, 58.55, 54.81, 53.82, 53.64, 52.61, 51.96, 12.68, 11.80 ppm. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{17}H_{30}N_3O$, 292.2389; found, 292.2384.



51

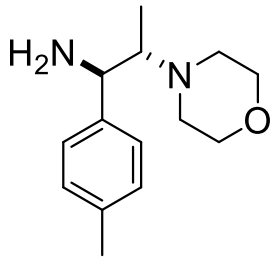
***N*-(4-methoxybenzyl)-2-(pyrrolidine-1-yl)propan-1-amine, 51**: The compound was prepared according to general procedure A using pyrrolidine (123 μL, 1.5 mmol, 3 equiv.) as the nucleophilic amine partner. The pale yellow oil (121.7 mg, 0.49 mmol) was obtained in 98% yield.

R_f = 0.62 (1:9 $NH_4OH/CHCl_3$). ^1H NMR (C_6D_6, 500 MHz): δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.72 (s, 2H), 3.32 (s, 3H), 2.66-2.51 (m, 3H), 2.43-2.36 (m, 4H), 2.18 (br s, 1H), 1.59-1.53 (m, 4H), 1.08 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz) δ 159.22, 133.58, 129.59, 114.05, 57.82, 54.79, 54.02, 53.99, 50.27, 23.93, 15.61 ppm. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1967.



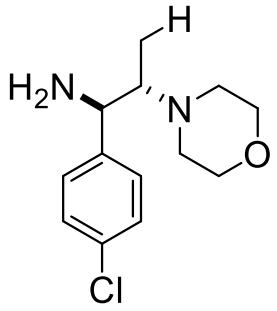
2-morpholino-1-phenylpropan-1-amine: The general primary allyl amine hydroamination procedure B was followed using allyl amine (67 mg, 0.50 mmol, 1.00 equiv.) and morpholine (87 μL, 1.0 mmol, 2.0 equiv., freshly distilled). Diamine was isolated as a pale yellow oil in 84% yield (93 mg, 0.42 mmol).

^1H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 4.16 (d, *J* = 4.4 Hz, 1H), 3.66 (ddd, *J* = 5.4, 3.7, 1.4 Hz, 4H), 2.63 (qd, *J* = 6.8, 4.4 Hz, 1H), 2.51 (tq, *J* = 11.3, 5.7, 4.7 Hz, 4H), 2.47 (brs, 2H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz) δ 145.29, 128.25, 127.41, 126.79, 67.53, 65.89, 55.87, 51.19, 10.10 ppm. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{13}H_{21}N_2O$, 221.1654; found, 221.1645.



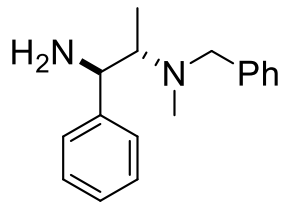
2-morpholino-1-(*p*-tolyl)propan-1-amine: The general primary allyl amine hydroamination procedure B was followed using allyl amine (125 mg, 0.85 mmol, 1.00 equiv.) and morpholine (223 μL, 1.2 mmol, 3.0 equiv., freshly distilled) and was run for 24 hours. Diamine was isolated as a clear oil in 83% yield (165 mg, 0.71 mmol).

^{1}H NMR (C_6D_6, 500MHz) δ 7.28 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 3.97 (d, *J* = 4.3 Hz, 1H), 3.59 – 3.48 (m, 4H), 2.30 (td, *J* = 6.7, 4.6 Hz, 1H), 2.25 (t, *J* = 4.6 Hz, 4H), 2.19 (s, 3H), 1.24 (s, 2H), 0.82 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 142.32, 136.01, 128.98, 127.37, 67.58, 65.98, 55.60, 51.28, 21.14, 10.14 ppm. HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1804.



1-(4-chlorophenyl)-2-morpholinopropan-1-amine: The general primary allyl amine hydroamination procedure B was followed using allyl amine (64 mg, 0.38 mmol, 1.00 equiv.) and morpholine (70 μL, 0.8 mmol, 2.0 equiv., freshly distilled). Diamine was isolated as a clear oil in 81% yield (78 mg, 0.31 mmol)

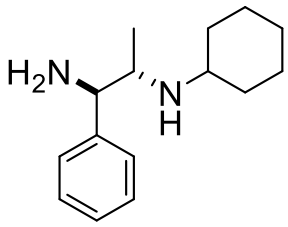
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.19 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 3.74 (d, *J* = 4.6 Hz, 1H), 3.52 – 3.47 (m, 4H), 2.17 (dd, *J* = 5.4, 3.1 Hz, 4H), 2.15 – 2.09 (m, 1H), 1.06 (s, 2H), 0.69 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, Benzene) δ 143.89, 132.37, 128.81, 128.33, 67.46, 65.67, 55.33, 51.07, 9.98.



(1R,2S)-N^2-benzyl-N^2-methyl-1-phenylpropane-1,2-diamine: [(DPEphos)Rh(COD)]BF_4 (8.5 mg, 0.010 mmol, 5.0 mol %), allyl amine (54 mg, 0.40 mmol, 1.0 equiv.), and dry CH_3CN (100 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added *N*-methyl-*N*-benzylamine (242 mg, 2.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to

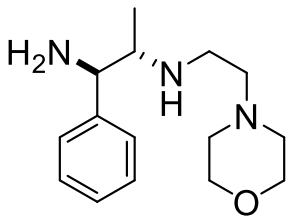
room temperature. The reaction mixture was then concentrated *in vacuo* to afford the crude diamine as yellow oil. Purification of the crude diamine by silica gel chromatography (10 g silica, 100% $CHCl_3$ to 3% NH_4OH : 97% $CHCl_3$ to 3% NH_4OH : 3% MeOH: 97% $CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine as a pale yellow oil in 31% yield (32 mg, 0.13 mmol).

R_f = 0.35 (1:9 NH_4OH /CHCl3). ^1H NMR (C_6D_6, 500 MHz) δ 7.22 (d, J = 6.8 Hz, 4H), 7.14 (d, J = 8.3 Hz, 8H), 7.11 – 7.04 (m, 4H), 3.77 (d, J = 6.9 Hz, 1H), 3.41 (d, J = 13.6 Hz, 1H), 3.34 (d, J = 13.6 Hz, 1H), 2.67 (p, J = 6.7 Hz, 1H), 1.98 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.38, 140.15, 128.63, 128.19, 128.16, 127.16, 126.76, 126.74, 63.87, 59.10, 58.72, 37.90, 10.02. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{17}H_{23}N_2$, 255.1861; found, 255.1862.



N^2-cyclohexyl-1-phenylpropane-1,2-diamine: The general primary allyl amine hydroamination procedure C was followed using allyl amine (54 mg, 0.40 mmol, 1.0 equiv.) and *N*-cyclohexylamine (200 mg, 2.0 mmol, 5.0 equiv.). Diamine was isolated as a pale yellow oil in 66% yield (62 mg, 0.27 mmol).

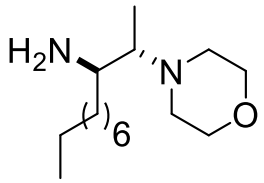
R_f = 0.12 (1:9 NH_4OH /CHCl3). ^1H NMR (C_6D_6, 500 MHz) δ 7.34 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.89 (d, J = 4.0 Hz, 1H), 2.94 (qd, J = 6.4, 4.2 Hz, 1H), 2.43 (tt, J = 10.0, 3.7 Hz, 1H), 1.85 – 1.45 (m, 13H), 1.20 – 1.04 (m, 5H), 1.02 – 0.90 (m, 4H), 0.85 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, Benzene) δ 144.84, 128.28, 127.65, 126.89, 59.08, 55.60, 53.94, 34.56, 34.23, 26.61, 25.47, 25.33, 15.89. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{15}H_{25}N_2$, 233.2018; found, 233.2013.



N^2-(2-morpholinoethyl)-1-phenylpropane-1,2-diamine: The general primary allyl amine hydroamination procedure C was followed using allyl amine (54 mg, 0.40 mmol, 1.0 equiv.) and 2-morpholinoethylamine (260

mg, 2.0 mmol, 5.0 equiv.). Diamine was isolated as a pale yellow oil in 58% yield (62 mg, 0.24 mmol).

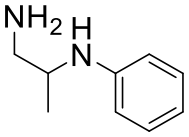
R_f = 0.28 (1:9 NH_4OH /CHCl3). ^1H NMR (C_6D_6, 500 MHz) δ 7.33 (d, J = 7.2 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 3.82 (d, J = 5.0 Hz, 1H), 3.47 (q, J = 4.1 Hz, 4H), 2.73 – 2.65 (m, 1H), 2.57 – 2.50 (m, 1H), 2.44 (ddd, J = 11.7, 6.8, 5.3 Hz, 1H), 2.28 – 2.14 (m, 3H), 2.07 (t, J = 4.4 Hz, 4H), 1.43 (s, 3H), 0.95 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, Benzene) δ 144.96, 128.39, 127.66, 127.04, 67.11, 59.96, 59.28, 58.60, 53.90, 44.33, 15.75. HRMS (ESI-TOF) *m/z*: [M+H^+] calculated for $C_{15}H_{26}N_3O$, 264.2076; found, 264.2084.



2-morpholinoundecan-3-amine: The general primary allyl amine hydroamination procedure B was followed using allyl amine (85 mg, 0.50 mmol, 1.00 equiv.) and morpholine (175 μL, 2.0 mmol, 4.0 equiv., freshly distilled) and was run for 24 hours. (175 μL, 2.0 mmol, 4.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. Diamine was isolated as a clear oil in 80% yield (103 mg, 0.40 mmol).

^1H NMR (C_6D_6, 500 MHz) δ 3.59 (ddd, *J* = 5.3, 3.9, 2.5 Hz, 4H), 2.68 (ddd, *J* = 8.2, 5.2, 3.0 Hz, 1H), 2.27 (tq, *J* = 11.0, 6.3, 5.0 Hz, 4H), 1.96 (qd, *J* = 6.6, 5.2 Hz, 1H), 1.48 (dd, *J* = 7.5, 3.0 Hz, 2H), 1.40 – 1.26 (m, 11H), 1.21 (dt, *J* = 10.0, 8.2 Hz, 1H), 0.97 – 0.88 (m, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.77(s, 2H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ 67.62, 64.37, 52.18, 50.80, 35.42, 32.39, 30.45, 30.18, 29.87, 27.05, 23.17, 14.42, 9.52 ppm. HRMS (ESI-TOF) *m/z*: [M+H^+] calcd for $C_{15}H_{33}N_2O$, 257.2593; found, 257.2595.

2.8.3 Hydroamination of allyl amine with aniline



To a 4 mL vial equipped with stir bar was added $[Ir(cod)Cl]_2$ (6.72 mg, 0.010 mmol, 1.0%), BINAP (16 mg, 0.025 mmol, 2.5%), toluene (500 μL, 2 M), allyl amine (75 μL, 1.0 mmol, 1.0

equiv.), and aniline (457 μL, 5 mmol, 5 equiv.). The 4 mL vial was sealed with Teflon cap, removed from nitrogen filled glove box, heated to 120 °C for 1 minute, cooled to room temperature, returned to the glove box, uncapped, and LiI (134 mg, 1.0 mmol, 1 equiv.) was added. The 4 mL vial was again sealed with Teflon cap, removed from glove box, and heated to 120 °C for 6 h. The reaction mixture was then cooled to room temperature and *ca* 1 mL each of $CHCl_3$ and half-saturated K_2CO_3 were added. The biphasic mixture was sonicated (with cap on) for 15 minutes, the mixture was dissolved up in *ca* 30 mL half-saturated K_2CO_3, and extracted 3 x 50 mL $CHCl_3$. The organic layers were dried with $MgSO_4$, filtered, and the concentrated by rotary evaporation. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3:0:97 to 3:8:89 NH_4OH:MeOH:$CHCl_3$ v/v prepared by extracting saturated NH_4OH with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine as a pale yellow oil in 80% yield (119 mg, 0.80 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 (dd, *J* = 8.6, 7.2 Hz, 2H), 6.72 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 2H), 3.53 (dq, *J* = 12.7, 6.3 Hz, 1H), 2.86 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.75 (dd, *J* = 12.8, 6.1 Hz, 1H), 1.78 – 1.26 (br s, 2H), 1.20 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.65, 129.25, 117.22, 113.37, 50.70, 47.24, 18.46.

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Chapter 3

Intermolecular Regioselective Hydroamination of Homoallylic Amines with Electron Rich Amine Nucleophiles to Form 1,4-Diamines

3.1 Introduction

The 1,4-relationsip between an amine and Lewis-basic site is common in natural products and biologically active compounds.[1–3] Common methods for the formation of this motif involve reductive aminations, nucleophilic displacements (such as S_N1 or S_N2 reactions), and the Stetter reaction.[4] While these are powerful methods in organic chemistry, they typically require several steps to first install oxidized moieties and then transform them into the desired C–N bond. The ability to rapidly assemble these motifs from readily accessible starting materials (such as homoallylic Lewis-basic sites and amine nucleophiles) with complete atom economy would represent an orthogonal and single-step approach to this building block. Some biologically active compounds that could be formed with this proposed approach are illustrated (Figure 3.1).

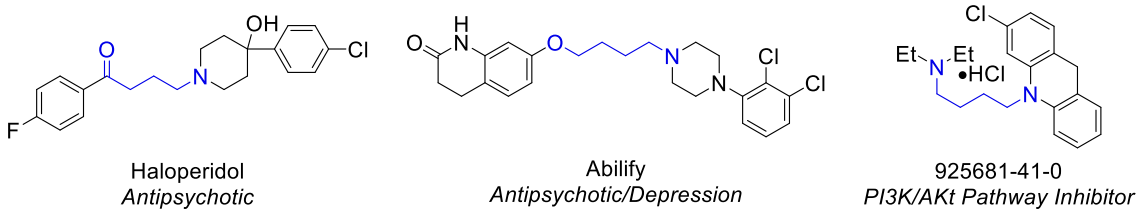
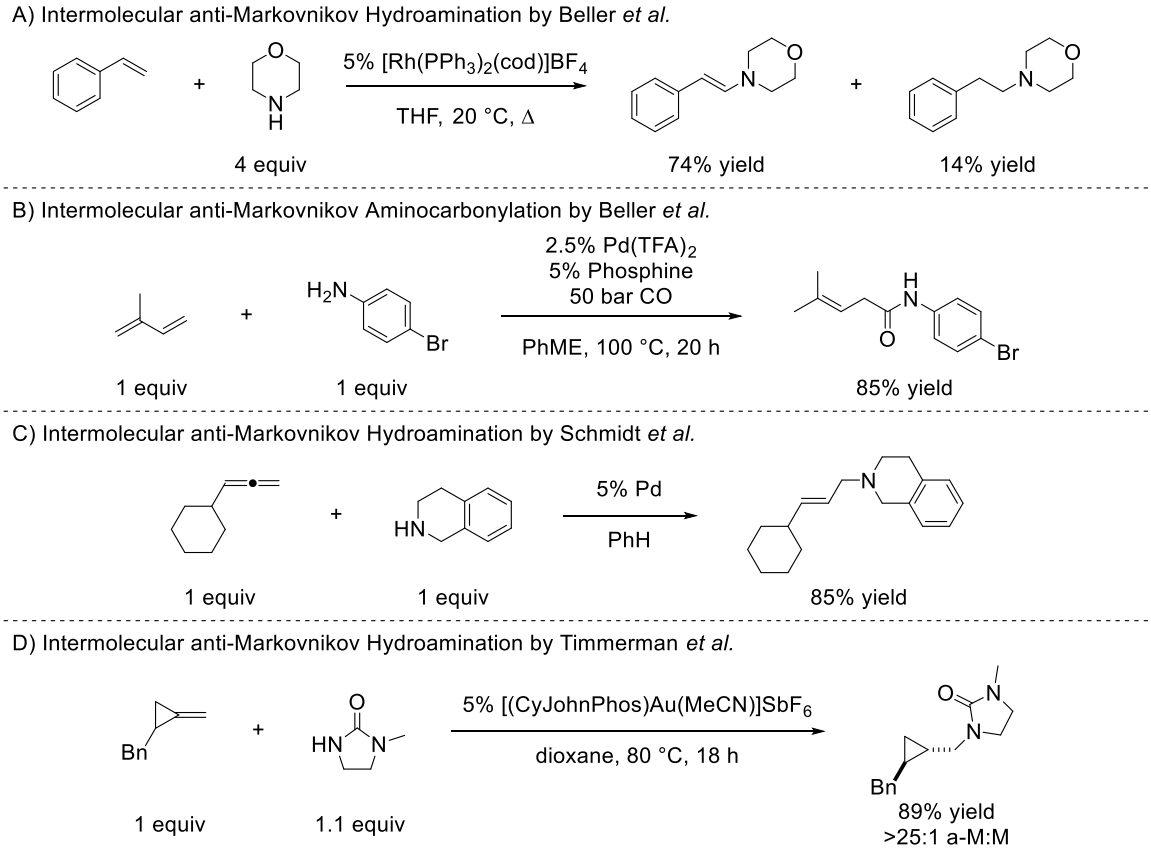


Figure 3.1: Some Biologically Active Compounds that Could be Synthesized *via* the Anti-Markovnikov Hydroamination of Homoallylic Lewis-Basic Substrates.

Hydroamination, or the addition of an amine across an unsaturated C–C bond, couples two readily accessible functional groups with complete atom economy to form (with terminal or 1,1,2-trisubstituted alkenes) either Markovnikov or anti-Markovnikov products, if the new C–N bond is installed to form the branched or linear product respectively.[5–9] With late transition metal catalysts, the regioselectivity of this reaction is typically governed by the substrate. When alkenes bearing aliphatic substituents are subjected to late transition metal mediated hydroamination conditions, Markovnikov products are typically observed.[10,11] In contrast, activated alkenes are usually required to form the products of anti-Markovnikov hydroamination. For example, when vinyl arenes are subjected to similar conditions, anti-Markovnikov products are usually observed

(Scheme 3.1:A).[12–15] Additionally, the anti-Markovnikov hydrofunctionalization of other activated alkenes, such as 1,3-dienes (Scheme 3.1:B),[16,17] allenes (Scheme 3.1:C),[18,19] or methylenecyclopropanes (Scheme 3.1:D)[20] has been reported. As such, the anti-Markovnikov hydroamination of unactivated aliphatic terminal alkenes is considered a significant challenge in organometallic chemistry.

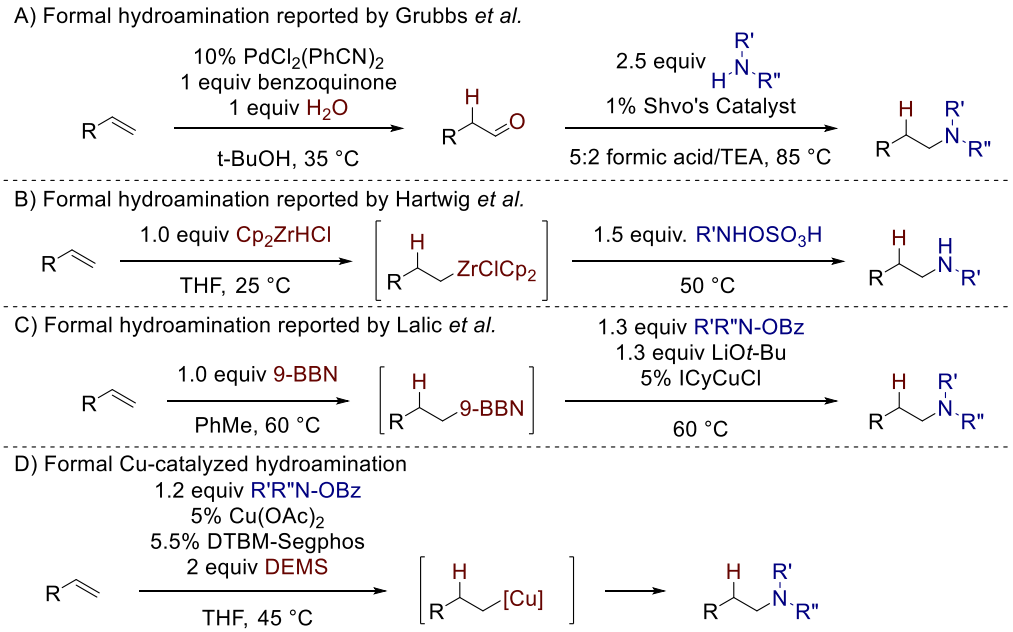
Scheme 3.1: Anti-Markovnikov Hydrofunctionalization Reports.



To obviate issues associated with substrate controlled anti-Markovnikov hydroamination, methods that allow for the formal transformation on terminal alkenes have been reported. Work by Grubbs and coworkers features the two-step aldehyde selective Wacker oxidation of terminal alkenes followed by reductive amination with Shvo's catalyst (Scheme 3.2:A).[21] The two-step hydrozirconation/amination of terminal alkenes has been disclosed by Hartwig *et al* (Scheme 3.2:B).[22] Similarly, Lalic and coworkers have reported a sequential hydroboration/Cu-catalyzed amination reaction (Scheme 3.2:C).[23] The mechanism of the second step of this transformation involves *i.* activation of the 9-BBN moiety in the presence of base, *ii.* transmetalation of the activated 9-BBN to the Cu-catalyst, *iii.* oxidative addition by the Cu^{I} into the benzoyl amine and

iv. reductive elimination to form the desired C–N bond. This work laid the foundation for an active area in the formal hydroamination literature. Significant improvements on this transformation were advanced by Miura, Buchwald, and Hartiwig, and utilize a hydride source added in stoichiometric quantities which can react *in situ* with the copper catalyst (Scheme 3.2:D).[24–28] As such, this transformation was improved from a two-step process (hydroboration followed by a Cu-catalyzed reaction with an electrophilic amine source) to a one-step process. Further extensions of this single-step methodology involve the asymmetric hydrometallation/amination of disubstituted terminal alkenes and internal alkenes.[29]

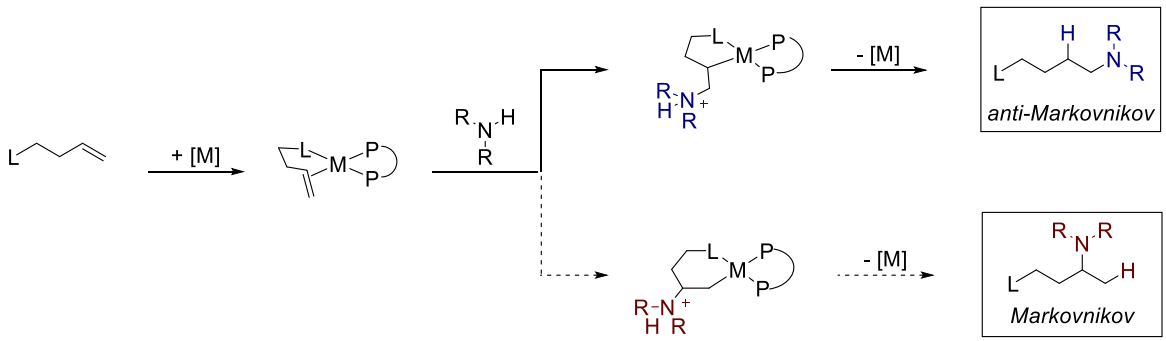
Scheme 3.2: Methods for Formal Anti-Markovnikov Hydroamination.



We have demonstrated (in Chapter 2) that a Rh-catalyzed hydroamination reaction can proceed *via* a five-membered metalacyclic intermediate to form Markovnikov products. Reactions involving the directed migratory insertion of a M–X species into an alkene have been reviewed.[30] Recent reports of directed functionalization have also been disclosed.[31–34] We reasoned that a system similar to the one that allowed for the Markovnikov hydroamination of allylic amines and imines might, with a homoallylic Lewis-basic motif, we able to access a similar five-membered intermediate; this would allow for the formation of anti-Markovnikov products (Scheme 3.3). Computational studies have demonstrated that, in some cases, the five-membered metallacycle be significantly favored over the six.[35,36] It is worth noting that a four-membered metallacycle should

be significantly more strained than five- and, for that reason, we did not begin our studies by working to effect anti-Markovnikov hydroamination on allylic amines or imines.

Scheme 3.3: Mechanistic Rationale for the Anti-Markovnikov Hydroamination of Homoallylic Amines



3.2 Hydroamination of α,α-disubstituted Substrates with Electron Rich Nucleophiles

3.2.1 Optimization

The ability of homoallylic amines and imines to undergo a rhodium-catalyzed hydroamination reaction with a variety of electron rich secondary cyclic amine nucleophiles was evaluated in conjunction with Mr. Evan Vanable. Explorations began with α,α-disubstituted homoallylic amines as it was reasoned that the substitution on these substrates may, *via* the Thorpe-Ingolde effect, bias them towards the reactive κ^3 conformation;[37] the bulk of this screening was carried out with test substrate **1** and morpholine, **2**, as the nucleophile (Table 3.1).

The reaction was optimized by varying time, temperature, ligand, and solvent. While 60 °C had been sufficient for Markovnikov-selective conditions, higher temperatures were required for anti-Markovnikov selective conditions (Table 3.1: 1-4). However, when the reaction was run at temperatures at or above 140 °C, yields decreased significantly. The optimal temperature for this substrate and nucleophile was 100 °C. A variety of solvents were evaluated; excellent yields for the desired product were observed with all solvents except acetonitrile (Table 3.1: 5-9). The Lewis-basic site on the solvent likely inhibits the ability of the substrate to bind in a κ^3 and slows the rate of the reaction. Wider bite angle ligands (such as DPEphos, Figure 3.2) were far more effective at catalyzing the reaction than narrower bite angle[38,39] ligands like dppe, dppp, and dppb (Table 3.1: 9-12). A variety of silver salts were also evaluated. However, these had a far less pronounced effect on yields and selectivities with α,α-disubstituted substrates than the other

homoallylic amines discussed in this chapter. Finally, under all the Rh-catalyzed conditions examined, **1** underwent the intermolecular hydroamination reaction in >20:1 selectivity for the desired product.

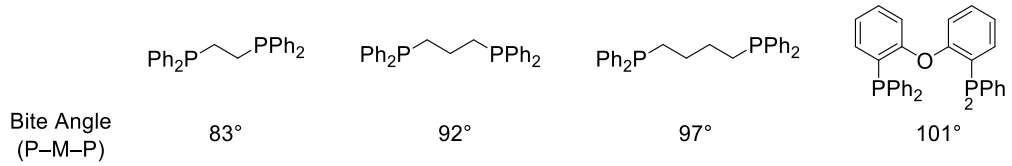
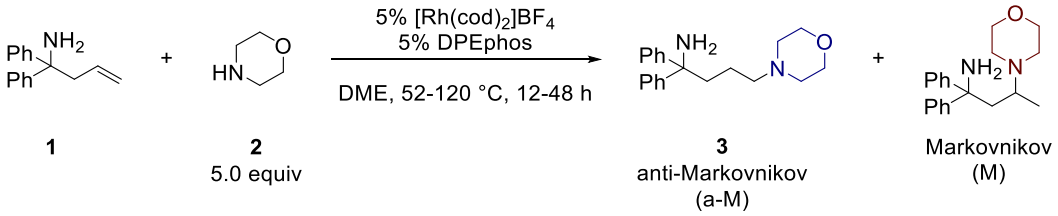


Figure 3.2: Selected Bite Angles of Bidentate Phosphine Ligands.

Table 3.1: Selected Optimization for the Rh-Catalyzed Hydroamination of **1** with **2**.

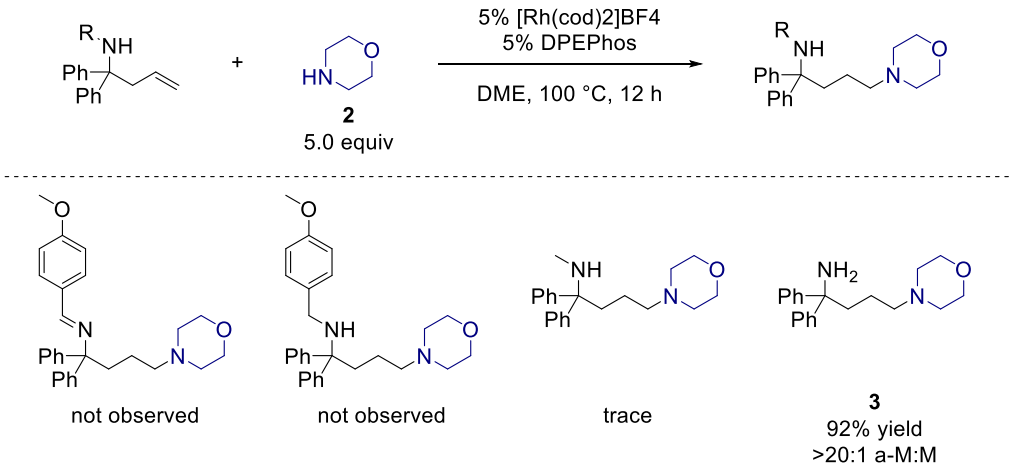


Entry	Temperature (°C)	Time (h)	Solvent	Ligand	GC Yield (%)	Selectivity (a-M:M)
1	40	48	DME	DPEphos	6.8	>20:1
2	80	24	DME	DPEphos	84	71:1
3	100	12	DME	DPEphos	92	43:1
4	120	12	DME	DPEphos	84	25:1
5	100	24	p-Dioxane	DPEphos	92	41:1
6	100	24	THF	DPEphos	90	42:1
7	100	24	PhMe	DPEphos	88	41:1
8	100	24	MeCN	DPEphos	66	20:1
9	100	24	DME	DPEphos	92	45:1
10	100	24	DME	dppe	9.2	45:1
11	100	24	DME	dppp	16	48:1
12	100	24	DME	dppb	17	31:1

Under optimized reaction conditions, formation of the desired 1,4-diamine was observed only with primary homoallylic amines and not in appreciable yields with secondary homoallylic

amines or imines (Table 3.2). While poor conversion of starting material was observed with secondary homoallylic amines, this is not the case with homoallylic imines. Instead, these substrates undergo a Rh-catalyzed aza-Claisen rearrangement,[40] in good yield, to form a product that is otherwise unreactive under reaction conditions. This transformation has been reported with similar catalysts.[41–43] With optimized conditions in hand for the anti-Markovnikov hydroamination of homoallylic amines, we proceeded to evaluate the scope of this transformation.

Table 3.2: Alternative Substrate for Anti-Markovnikov Intermolecular Hydroamination.

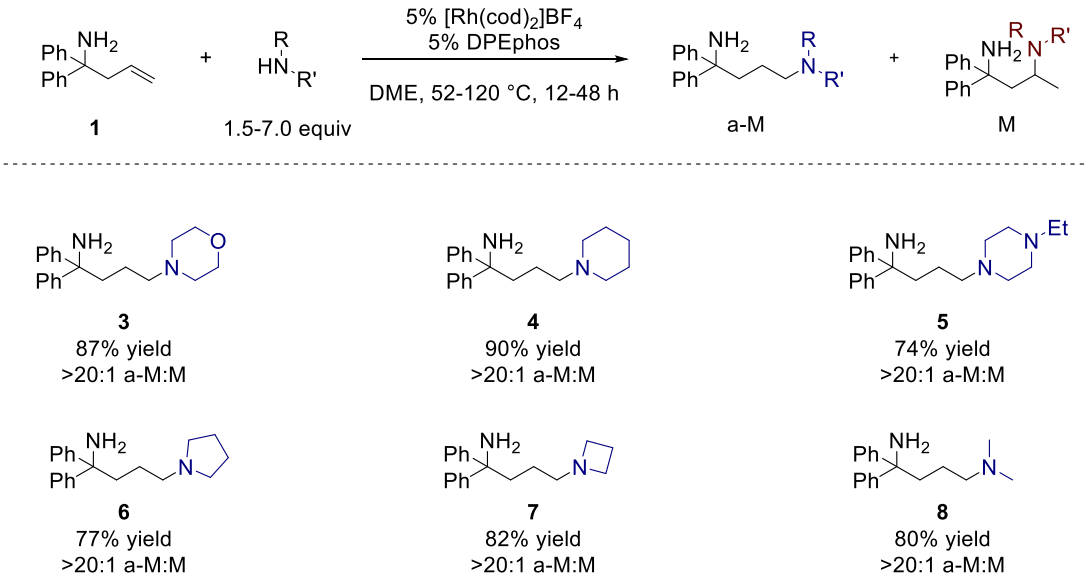


3.2.2 Scope

The scope of the transformation for the anti-Markovnikov hydroamination of α,α-disubstituted homoallylic amines was evaluated.[37] Gratifyingly, high selectivity was often observed for anti-Markovnikov product over the Markovnikov product.

A variety of cyclic secondary amines are well tolerated under reaction conditions. Morpholine, 1-ethylpiperazine, pyrrolidine, azetidine, and piperidine all give the desired product (**3-7**) in excellent yield and >20:1 regioselectivity with **1** (Table 3.3). Additionally, the secondary acyclic amine nucleophile dimethyl amine (**8**) can be employed under reaction conditions (Table 3.3). Gratifyingly, less forcing conditions can be employed in some cases. For example, azetidine undergoes the hydroamination at 52 °C (a temperature 5 °C below the boiling point of the amine) and fewer than 5 equivalents of pyrrolidine are required for the reaction.

Table 3.3: The Rh-Catalyzed Hydroamination of **1** with Secondary Amine Nucleophiles.

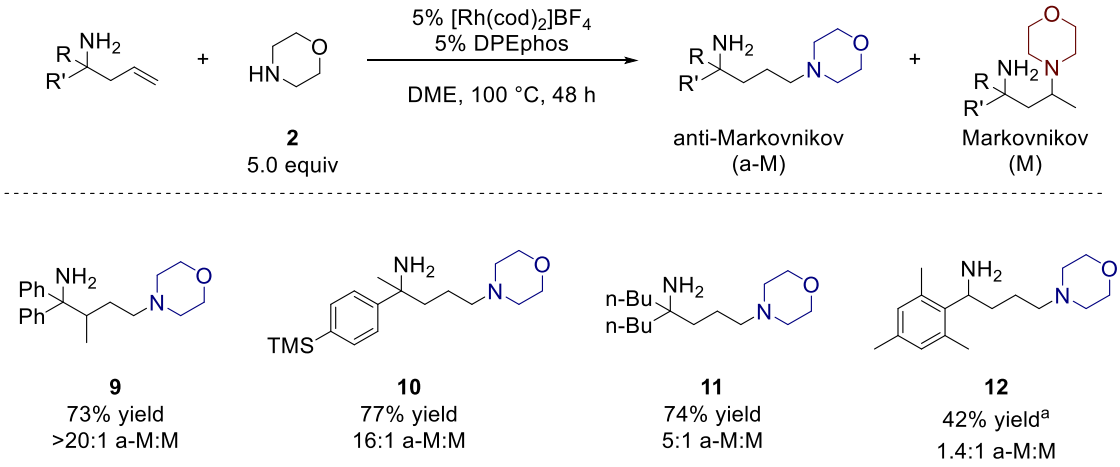


3.3 Hydroamination of α-substituted Homoallylic Amines and Homoallyl Amine with Electron Rich Nucleophiles

3.3.1 Challenges and Re-optimization

The substrate scope of the anti-Markovnikov hydroamination was then evaluated. Interestingly, the α,α,β-trisubstituted substrate **9** undergoes the hydroamination reaction with no appreciable decrease in regioselectivity. One might have anticipated that the added steric bulk would erode the selectivity of the reaction. However, decreasing bulk at the α-position does erode selectivity (Table 3.4). While **9** undergoes the reaction with excellent selectivity, the acetophenone derived substrate gives a 16:1 a-M:M selectivity. Further removing steric bulk from the α-position (as shown with the α,α-dibutyl substrate, **10**) gives a mixture of 1,4- and 1,3-diamines with a 5:1 selectivity for the desired anti-Markovnikov product **11**. Finally, when α-mesityl homoallyl amine (**13**) is subjected to reaction conditions, little selectivity is observed for either regioisomer.

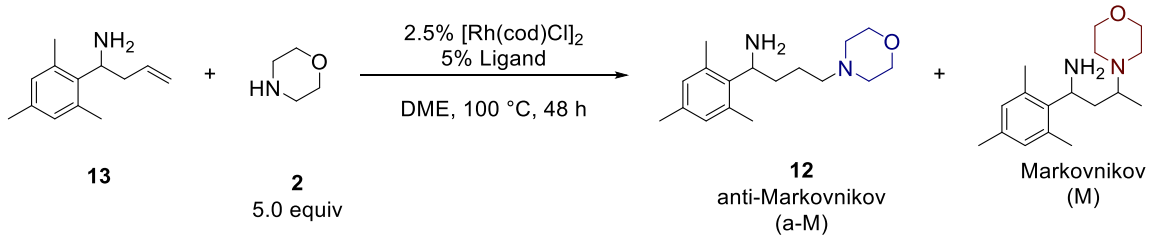
Table 3.4: The Effect of Decreasing Steric Bulk at the α-Position of the Homoallylic Amine on the Selectivity of the Reaction.



[a]The reaction was stirred for 72 h at 120 °C.

The reduced selectivity was likely caused by a decrease in the energy difference of the two transition states associated with either the five or six membered metallacycle. We reasoned that screening alternative phosphine ligands may restore the selectivity of the reaction with α-substituted substrates. The relatively bulky α-mesitylhomoallyl amine (**13**) was used as a model substrate and morpholine (**2**) as the nucleophile. Gratifyingly, smaller bite angle ligands (Figure 3.2) improved both yields and selectivities for this reaction (Table 3.5: entries 1-6). Additionally, the counter-ion associated with the cationic rhodium catalyst does influence the outcome of the reaction (Table 3.5: entries 7-11). Reoptimized conditions (for α-substituted substrates) feature the *in situ* formed [Rh(dppp)(cod)]OTs.

Table 3.5: Selected Optimization for the Anti-Markovnikov Hydroamination of α-Substituted Homoallyl Amine.



13 | **2** 5.0 equiv | **12** anti-Markovnikov (a-M) | Markovnikov (M)

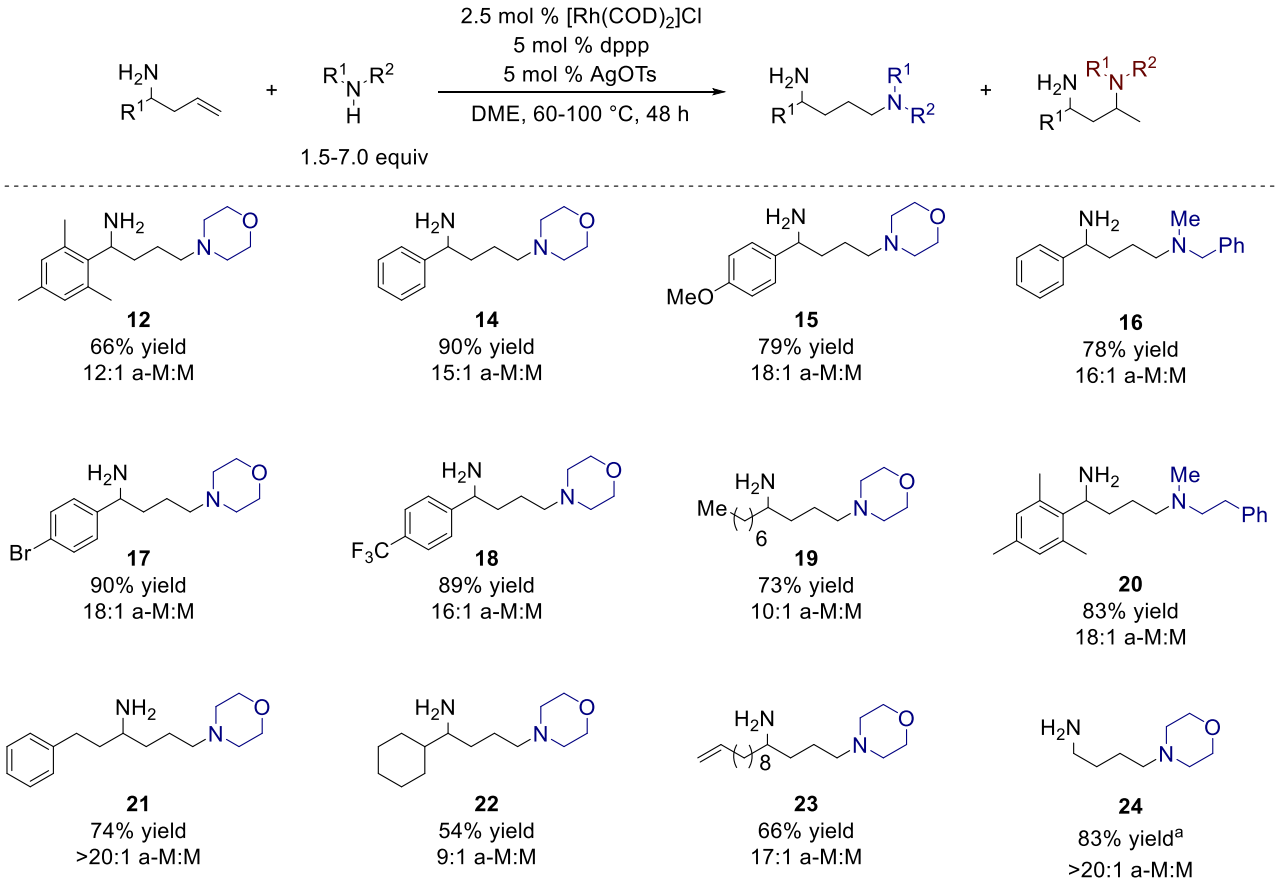
Entry	Ligand	[Ag] Salt	Morpholine Equiv	GC Yield (%)	Selectivity (a-M:M)
1	dppm	$AgBF_4$	5	<5	1.7:1
2	dppe	$AgBF_4$	5	<5	2.7:1
3	dppp	$AgBF_4$	5	68	14:1
4	dppb	$AgBF_4$	5	41	5.2:1
5	dppf	$AgBF_4$	5	<5	2.2:1
6	DPEphos	$AgBF_4$	5	<5	1.2:1
7	dppp	AgTFA	5	55	10:1
8	dppp	$AgSbF_6$	5	66	9.0:1
9	dppp	$AgPF_6$	5	66	7.5:1
10	dppp	AgOMs	5	59	10:1
11	dppp	AgOTs	5	86	37:1
12	dppp	AgOTs	7	92	27:1
13	dppp	AgOTs	3	67	54:1
14	dppp	AgOTs	2	67	46:1

3.3.2 Scope

The scope for the anti-Markovnikov hydroamination of α-substituted homoallylic amines was evaluated (Table 3.6). Excitingly, bulky aryl substituents (**12**), less bulky aliphatic substituents (**19** & **21**), and homoallyl amine (**24**) give predominantly the 1,4-diamine product. Aryl bromides (**17**) and distal alkenes (**23**) are well tolerated. Electron rich (**15**) and electron poor (**18**) substituents can be employed at the α-position of the homoallylic amine. Finally, these conditions are demonstrated with both secondary cyclic amines (morpholine and pyrrolidine) and

secondary acyclic nucleophiles including methylphenethyl amine (**20**) and methylbenzyl amine (**16**). When primary amines are subjected to reaction conditions, deallylation of the substrate to form an aldimine, followed by condensation of the amine nucleophile with loss of ammonia, is frequently observed.

Table 3.6: 1,4-Diamines Formed from the Anti-Markovnikov Hydroamination of Homoallylic Amines.



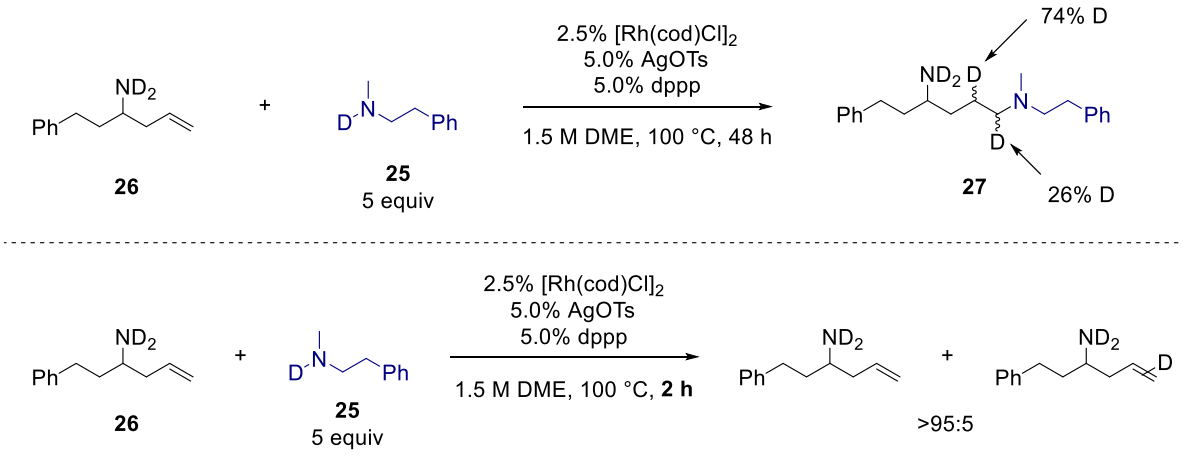
[a]$AgBF_4$ instead of AgOTs. Protected with Boc_2O prior to isolation.

3.4 Mechanistic Studies

3.4.1 Deuterium Incorporation Studies

Deuterium incorporation experiments were conducted under conditions for the hydroamination of α-substituted substrates. As had been previously observed with the hydroamination of *N*-allyl imines, no H/D exchange was observed into the C–H bond adjacent to the amine directing group.[44] When α-phenylhomoallyl amine is subjected to reaction conditions, ortho-deuteration of the aryl ring is observed, likely by a C–H activation pathway; this is not observed when aliphatic substituents are located at the α-position. Additionally, when deuterated amine nucleophile **25** is subjected to reaction conditions, deuteration of the C–H bonds of the nucleophile is not observed. Rather, the deuterium is incorporated solely into the substrate **26** to give **27**. Finally, when the reaction is run to *ca* 20% yield, no deuteration of **26** is observed. These results are summarized (Scheme 3.4).

Scheme 3.4: Deuterium Incorporation Studies on α-Phenethylhomoallyl Amine.



^{2}H NMR for the Rh-catalyzed hydroamination of α-phenethylhomoallyl amine with methylphenethyl amine confirms that the deuterium is incorporated solely into the labeled positions of **27** (Scheme 3.4 and Figure 3.3). It is worth noting that the deuterium label is incorporated into both positions of the alkene. This would suggest that, following the aminometalation step, β-hydride elimination and reinsertion can occur. Interestingly, this is not observed with the allylic amine system[44] and suggests that exocyclic β-hydride elimination can occur at a far faster rate than in the endocyclic case.

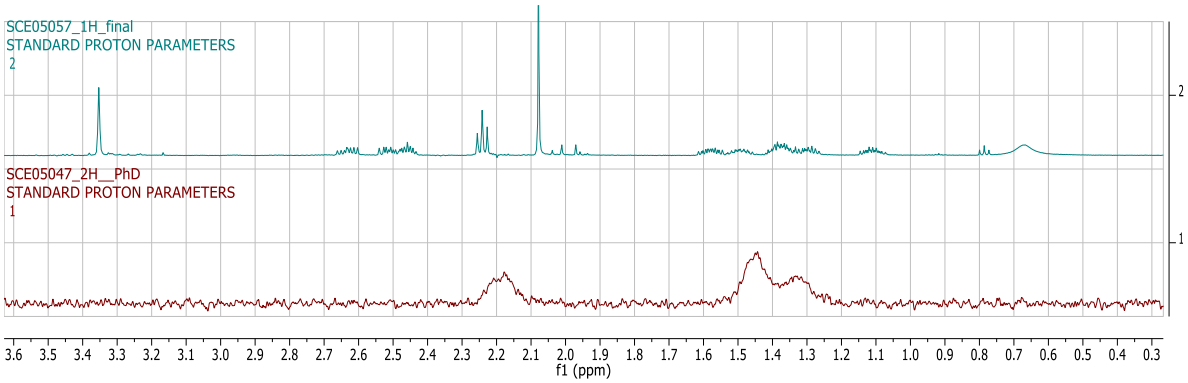
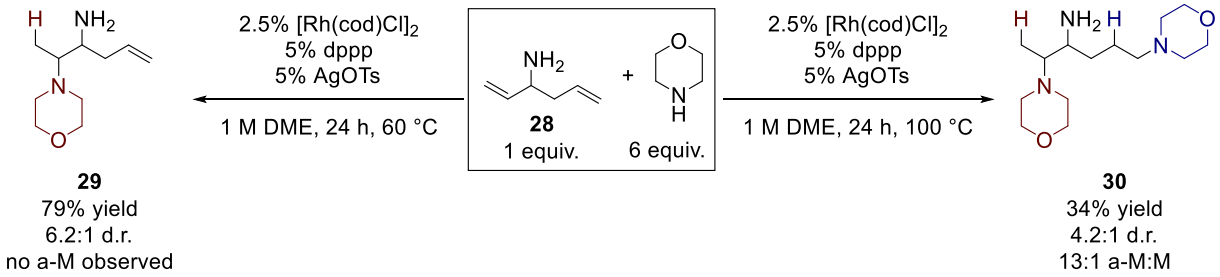


Figure 3.3: Deuterium Incorporation Occurs solely into the Terminal Alkene during the Hydroamination Reaction. Both the ^{1}H (blue) and ^{2}H (red) NMR Spectra are Shown.

3.4.2 Competition Substrate

The rate at which the hydroamination reaction proceeds for allylic and homoallylic amines was evaluated. The intramolecular competition substrate **28** was synthesized and subjected to reaction conditions optimized for the hydroamination of α-substituted homoallylic amines (Scheme 3.5). Under more mild conditions (when the reaction was performed at 60 °C), only functionalization of the allylic motif was observed to give **29**. This is consistent with what had been observed when optimizing Markovnikov and anti-Markovnikov selective reaction conditions; while the 1,2-diamine forms rapidly at 60 °C, the 1,4-diamine product does not. Under more forcing conditions (when the reaction is run at 120 °C), hydroamination of both the allylic and homoallylic motif is observed to obtain **30**. Considering these two results, this suggests that the hydroamination of allylic amines proceeds at a much faster rate than the hydroamination of homoallylic amines.

Scheme 3.5: Conditions for the Markovnikov-Selective Hydroamination of **28** and the Formation of Triamine Product **30**.



3.5 Conclusion

The ability of homoallylic primary amines, in conjunction with a Rh-catalyst, to reverse the inherent regioselectivity of a hydroamination reaction has been reported. This substrate-controlled system predominantly accesses a five-membered metalacylic intermediate to form 1,4-diamines and anti-Markovnikov products. The substitution pattern on the homoallylic amine and the ligand ligated to the rhodium catalyst influence the ratio of anti-Markovnikov to Markovnikov products formed. Related work in the field has applied this directed approach towards the palladium-catalayzed hydroamination and hydrocarbonation of β,γ-unsaturated amides featuring 8-aminoquinoline directing groups.[45,46]

Ongoing work will study the mechanism of this reaction and work to broaden the scope of the reaction to alternative directing groups. Additionally, promising initial results have shown that the selectivity of this reaction can be significantly eroded. This suggests that it may be possible to effect either Markovnikov or anti-Markovnikov hydroamination selectively on homoallylic amines simply by varying the catalyst. This is further explored with electron-deficient aryl amines in Chapter 4.

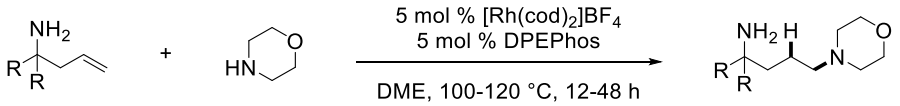
3.6 Experimental Procedure[47]

General Experimental Procedures: All reactions were carried out in flame-dried (or oven-dried at 140 °C for at least 2 h) glassware under an atmosphere of nitrogen unless otherwise indicated. Nitrogen was dried using a drying tube equipped with Drierite™ unless otherwise noted. Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level ~ 0.1 ppm). Column chromatography was performed with silica gel from Grace Davison Discovery Sciences (35-75 μm) mixed as a slurry with the eluent and columns were packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on precoated glass silica gel plates (by EMD Chemicals Inc.) with F-254 indicator. Visualization was either by short wave (254 nm) ultraviolet light, or by staining with either ninhydrin or potassium permanganate followed by brief heating on a hot plate or by a heat gun. Distillations were performed using a 3 cm short-path column under reduced pressure or by using a Hickman still at ambient pressure.

Instrumentation: ^{1}H NMR and ^{13}C NMR were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for ^{13}C) or a VXR-500 MHz spectrometer. Spectra were referenced using either $CDCl_3$ or C_6D_6 as solvents (unless otherwise noted) with the residual solvent peak as the internal standard (^{1}H NMR: δ 7.26 ppm, ^{13}C NMR: δ 77.36 ppm for $CDCl_3$ and ^{1}H NMR: δ 7.15 ppm, ^{13}C NMR: δ 128.62 ppm for C_6D_6). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) p (pentet,) m (multiplet,) and br (broad). Coupling constants, *J*, are reported in Hertz and integration is provided, along with assignments, as indicated. Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at University of Illinois at Urbana-Champaign. The glove box, MBraun LABmaster sp, was maintained under nitrogen atmosphere. Melting points were recorded on a Barnstead Thermolyne Mel-Temp® capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer using KBr salt plates.

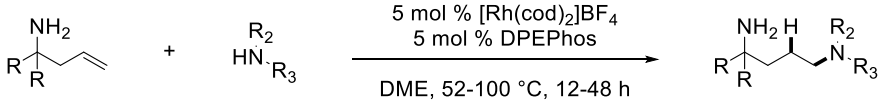
Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated stainless steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted. All amines (excluding homoallyl amine and dimethylamine) were distilled and degassed by the freeze-pump-thaw method and were stored under an atmosphere of nitrogen in glove box before use. Homoallylamine was obtained from Alfa Aesar and used as received**.** Dimethylamine solution was obtained from TCI and degassed by freezing, placing under vacuum, and refilling with nitrogen before thawing three times.

General Procedure for Hydroamination A:



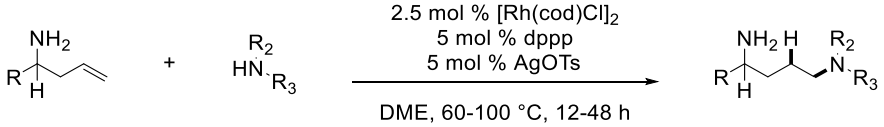
$[Rh(COD)_2]BF_4$ (10. mg, 0.025 mmol, 5.0 mol %), DPEphos (14 mg, 0.025 mmol, 5.0 mol %), DME (330 μL), and homoallyl amine (0.50 mmol, 1.0 equiv) were added to a 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (0.5-3.5 mmol, 1-7 equiv). The resulting solution was sealed with Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 120 °C. After 48 h, the reaction vial was cooled to room temperature and excess morpholine was removed *in vacuo* at 60 °C. Purification of the crude diamine by silica gel afforded pure diamine.

General Procedure for Hydroamination B:



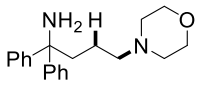
$[Rh(COD)_2]BAr_4^F$ (30. mg, 0.025 mmol, 5.0 mol %), DPEphos (27 mg, 0.050 mmol, 10. mol %), DME (330 μL), and homoallyl amine (0.5 mmol, 1.0 equiv) were added to a 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added amine nucleophile (0.5-3.5 mmol, 1-7 equiv). The resulting solution was sealed with Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 100 °C. After 48 h, the reaction vial was cooled to room temperature and excess amine was removed *in vacuo* at 60 °C. Purification of the crude diamine by silica gel chromatography afforded pure diamine.

General Procedure for Hydroamination C:



$[(COD)RhCl]_2$ (6.2 mg, 0.013 mmol, 2.5 mol %), dppp (10. mg, 0.025 mmol, 5.0 mol %), silver *para*-toluenesulfonamide (7.0 mg, 0.025 mmol, 5.0 mol %), DME (330 μL) and homoallyl amine

(0.50 mmol, 1.0 equiv) were added to an 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added amine nucleophile (0.50-3.5 mmol, 1.0-7.0 equiv). The resulting solution was sealed with Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 100 °C. After 48 h, the reaction vial was cooled to room temperature and morpholine was removed *in vacuo* at 60 °C. Purification of the crude diamine by silica gel chromatography afforded pure diamine.



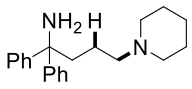
3

4-morpholino-1,1-diphenylbutan-1-amine, 3:

Prepared using general procedure **A** using: 1,1-diphenyl-but-3-en-1-amine (110 mg, 0.51 mmol, 1.0 equiv) and morpholine (220 μL, 2.5 mmol, 5.0 equiv). The reaction was run at 100 °C for 12 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **3** (140 mg, 0.44 mmol, 87% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.33 (10% MeOH : 90% CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 7.3 Hz, 4H), 7.28 (t, J = 7.7 Hz, 4H), 7.23 – 7.16 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 4.7 Hz, 4H), 2.39 – 2.21 (m, 8H), 1.80 (br s, 2H), 1.47 – 1.35 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.95, 128.33, 126.78, 126.54, 67.20, 61.19, 59.41, 53.94, 40.36, 21.53 ppm. IR (salt plate): 3368 (w, br), 3299 (w, br), 3084 (w, s), 3057 (m, s), 3022 (m, s), 2954 (s, br), 2854 (s, s) 2807 (s, s), 2765 (m, s), 1676 (w, br), 1598 (m, s), 1492 (m, s), 1446 (s, s), 1119 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H^+]$ calculated for $C_{20}H_{27}N_2O$, 311.2123; found, 311.2126.



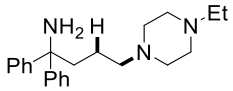
4

1,1-diphenyl-4-(piperidin-1-yl)butan-1-amine, 4:

Prepared using general procedure **A** using: 1,1-diphenyl-but-3-en-1-amine (110 mg, 0.50 mmol, 1.0 equiv) and piperidine (250 μL, 2.5 mmol, 5.0 equiv). The reaction was run at 100 °C for 12 h.

Analysis of the crude reaction mixture by gas chromatography determined a >20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **4** (140 mg, 0.45 mmol, 90.% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.14 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.1 Hz, 4H), 7.30 – 7.22 (m, 4H), 7.17 (t, J = 7.2 Hz, 2H), 2.26 (t, J = 7.6 Hz, 6H), 2.23 – 2.14 (m, 2H), 1.77 (br s, 2H), 1.52 (p, J = 5.5 Hz, 4H), 1.45 – 1.32 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.07, 128.30, 126.82, 126.47, 61.21, 59.93, 54.87, 40.77, 26.23, 24.74, 21.99 ppm. IR (salt plate): 3369 (w, br), 3298 (w, br), 3084 (w, s), 3057 (m, s), 3022 (m, s), 2933 (s, br), 2852 (m, s), 2799 (m, s), 2762 (m, br), 1669 (w, br), 1598 (m, s), 1492 (m, s), 1467 (m, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{21}H_{29}N_2$, 309.2331; found, 309.2331.



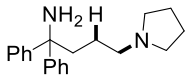
5

4-(4-ethylpiperazin-1-yl)-1,1-diphenylbutan-1-amine, 5:

Prepared using general procedure **A** using: 1,1-diphenyl-but-3-en-1-amine (110 mg, 0.50 mmol, 1.0 equiv) and 1-ethyl piperazine (320 μL, 2.5 mmol, 5.0 equiv). The reaction was run at 80 °C for 72 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **5** (130 mg, 0.37 mmol, 74% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.14 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, J = 8.3, 1.1 Hz, 4H), 7.31 – 7.24 (m, 4H), 7.18 (t, J = 7.3 Hz, 2H), 2.62 – 2.25 (m, 12H), 2.25 – 2.18 (m, 2H), 1.87 (br s, 2H), 1.45 – 1.31 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.10, 128.38, 126.87, 126.56, 61.26, 59.15, 53.48, 53.13, 52.64, 40.65, 21.97, 12.29 ppm. IR (salt plate): 3366 (w, br), 3290 (w, br), 3084 (w, s), 3057 (m, s), 3023 (m, s), 2966 (s, s), 2944 (s, br), 2875 (m, s), 2810 (s, br), 2770 (s, s), 1674 (w, br), 1598 (m, s), 1492 (m, s), 1465 (m, s), 1446 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{22}H_{32}N_3$, 338.2596; found, 338.2595.



6

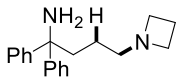
1,1-diphenyl-4-(pyrrolidin-1-yl)butan-1-amine, 6:

Prepared using general procedure **A** using: 1,1-diphenyl-but-3-en-1-amine (110 mg, 0.50 mmol, 1.0 equiv) and pyrrolidine (120 μL, 1.5 mmol, 3.0 equiv). The reaction was run at 60 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **6** ($1.0*10^2$ mg, 0.34 mmol, 67% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.12 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 8.3 Hz, 4H), 7.32 – 7.25 (m, 4H), 7.23 – 7.16 (m, 2H), 2.51 – 2.37 (m, 6H), 2.31 – 2.19 (m, 2H), 2.04 (br s, 2H), 1.80 – 1.71 (m, 4H), 1.45 (tt, J = 8.9, 6.0 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.07, 128.36, 126.88, 126.54, 61.26, 57.06, 54.47, 40.77, 24.09, 23.70 ppm. IR (salt plate):

3366 (w, br), 3297 (w, br), 3084 (m, s), 3057 (m, s), 3023 (m, s), 2956 (s, br), 2874 (s, s), 2786 (s, br), 1598 (m, s), 1492 (m, s), 1459 (m, s) cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H^+]$ calculated for $C_{20}H_{27}N_2$, 295.2174; found, 295.2173.



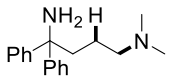
7

4-(azetidin-1-yl)-1,1-diphenylbutan-1-amine, 7:

Prepared using general procedure **A** using: 1,1-diphenyl-but-3-en-1-amine (110 mg, 0.50 mmol, 1.0 equiv) and azetidine (170 μL, 2.5 mmol, 5.0 equiv). The reaction was run at 52 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **7** (120 mg, 0.41 mmol, 82% yield of the major isomer, average of two runs) as a beige crystalline solid (m.p. 61-64 °C).

R_f = 0.07 (15% MeOH : 85% CH_2Cl_2). ^1H NMR (500 MHz, C_6D_6): δ 7.37 (d, J = 7.4 Hz, 4H), 7.12 (t, J = 7.7 Hz, 4H), 7.02 (t, J = 7.3 Hz, 2H), 2.92 (t, J = 6.8 Hz, 4H), 2.25 – 2.14 (m, 4H), 1.78 (p, J = 6.9 Hz, 2H), 1.52 (br s, 2H), 1.33 – 1.13 (m, 2H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ 150.47, 128.81, 127.68, 126.86, 61.57, 60.96, 55.83, 41.22, 23.18, 18.52 ppm. IR (salt plate): 3364 (w, br), 3288 (w, br), 3084 (w, s), 3057 (m, s), 3022 (m, s), 2994 (m, s), 2953 (s, s), 2926 (s, s), 2870 (m, s), 2816 (s, br), 1597 (m, br), 1492 (m, s), 1445 (m, s) cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H^+]$ calculated for $C_{19}H_{25}N_2$, 281.2018; found, 281.2011.



8

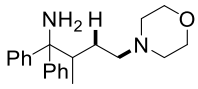
***N*^{4},*N*^{4}-dimethyl-1,1-diphenylbutane-1,4-diamine, 8:**

Prepared using general procedure **B** using: 1,1-diphenylbut-3-en-1-amine (91 mg, 0.41 mmol, 1 equiv) and dimethylamine (2 mL at 2.0 M solution in THF, 4.0 mmol, 10. equiv). The reaction

was run at 120 °C for 48 h. This reaction was run in a 15 mL heavy-walled schlenk tube behind a blast shield. Efforts to scale this reaction under general conditions were unreliable as the septa of the vial often failed. **Reactions under pressure can be a significant hazard if appropriate safety precautions, such as a blast shield, are not taken**.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 10% MeOH : 2.5% sat. NH_4OH : 87.5% $CHCl_3$ as the eluent) to afford **8** (88 mg, 0.33 mmol, 80.% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.08 (1:4 MeOH/DCM). ^1H NMR (C_6D_6, 500 MHz): δ 7.37 (dd, J = 8.4, 1.2 Hz, 4H), 7.12 (t, J = 7.85 Hz, 4H), 7.02 (tt, J = 7.3, 1.1 Hz, 2H), 2.21 – 2.15 (m, 2H), 2.10 (t, J = 6.7 Hz, 2H), 2.02 (s, 6H), 1.46 – 1.10 (m, 4H) ppm. ^{13}C NMR (C_6D_6 125 MHz): δ 150.47, 128.80, 127.67, 126.88, 61.54, 60.70, 46.10, 41.02, 23.31 ppm. IR (salt plate): 3367 (w, br), 3300 (w, br), 3084 (w, s), 3058 (m, s), 3022 (m, s), 2942 (s, br), 2856 (m, s), 2814 (s, s), 2765 (s, br), 2719 (w, s) 1598 (m, s), 1492 (m, s), 1456 (m, s), 1446 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [$M+H^+$] calculated for $C_{18}H_{25}N_2$: 269.2018; found, 269.2019.



9

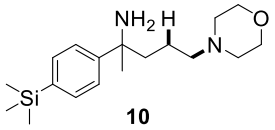
2-methyl-4-morpholino-1,1-diphenylbutan-1-amine, 9:

Prepared using general procedure **A** using: 2-methyl-1,1-diphenylbut-3-en-1-amine (140 mg, 0.61 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 5.8 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3%

MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **9** (140 mg, 0.44 mmol, 73% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.53 (15% MeOH : 85% CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 7.8 Hz, 2H), 7.25 (t, J = 8.1 Hz, 4H), 7.14 (t, J = 7.3 Hz, 2H), 3.70 (t, J = 4.7 Hz, 4H), 2.82 – 2.69 (m, 1H), 2.43-2.28 (m, 6H), 1.76 – 1.48 (m, 3H), 1.17 – 1.01 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.02, 147.93, 128.24, 128.23, 126.73, 126.61, 126.21, 126.10, 67.22, 64.41, 57.81, 54.14, 38.23, 29.00, 15.04 ppm. IR (salt plate): 3384 (w, br), 3317 (w, br), 3084 (w, s), 3056 (m, s), 3030 (m, s), 3021 (m, s), 2957 (s, br), 2854 (s, s), 2807 (s, s), 2766 (m, s), 1597 (m, s), 1491 (m, s), 1447 (s, s), 1118 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H^+]$ calculated for $C_{21}H_{29}N_2O$, 325.2280; found, 325.2278.



10

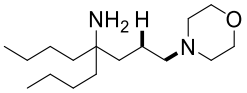
5-morpholino-2-(4-(trimethylsilyl)phenyl)pentan-2-amine, 10:

Prepared using general procedure **A** using: 2-(4-(trimethylsilyl)phenyl)pent-4-en-2-amine (120 mg, 0.52 mmol, 1.0 equiv) and morpholine (260 μL, 3.0 mmol, 6.0equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 16:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 70 mL of silica in a 3 cm diameter column, with 1% sat. NH_4OH : 99% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% sat. NH_4OH : 99% $CHCl_3$ as the eluent) to afford **10** (130 mg, 0.40 mmol, 77% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.09 (1:9 MeOH/DCM). ^1H NMR (C_6D_6, 500 MHz): δ 7.52 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 3.56 (t, J = 4.5 Hz, 4H), 2.06 (t, J = 4.5 Hz, 4H), 2.02 (td, J = 7.3, 1.4 Hz, 2H), 1.74 (ddd, J = 13.6, 11.8, 4.5 Hz, 1H), 1.57 (ddd, J = 13.5, 11.8, 4.7 Hz, 1H), 1.37-1.27 (m, 4H), 1.19 (tdd, J = 11.7, 9.0, 6.0 Hz, 3H), 0.23 (s, 9H) ppm. ^{13}C NMR (C_6D_6 126 MHz): δ 150.81, 138.10, 134.12, 125.89, 67.73, 60.01, 55.50, 54.67, 43.56, 32.77, 22.43, -0.38 ppm. IR (salt plate): 3364 (w, br), 3291 (w, br), 3068 (m, s), 3013 (m, s), 2955 (s, br) 2854 (s, s,), 2806 (s, s), 2764 (s, s),

1684 (m, s), 1599 (m, s),1248 (s, s), 1119 (s, s), 840 (br s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{18}H_{33}N_2OSi$: 321.2362; found, 321.2361.



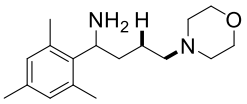
11

5-(3-morpholinopropyl)nonan-5-amine, 11:

Prepared using general procedure **A** using: 5-allylnonan-5-amine (74 mg, 0.40 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 7.0 equiv). The reaction was run at 120 °C for 72 h.

Analysis of the crude reaction mixture by gas chromatography determined a 5:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **11** (81 mg, 0.30 mmol, 74% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.11 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (t, J = 4.6 Hz, 4H), 2.45 (br s, 4H), 2.35 – 2.26 (m, 2H), 1.51 – 1.41 (m, 2H), 1.37 – 1.17 (m, 16H), 0.90 (t, J = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 67.29, 60.07, 54.15, 53.30, 40.30, 38.10, 26.01, 23.73, 21.05, 14.45 ppm. IR (salt plate): 3360 (w, br), 3284 (w, br), 2956 (s, br), 2931 (s, br), 2858 (s, s), 2807 (m, s), 2764 (m, s), 1560 (w, br), 1119 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{16}H_{35}N_2O$, 271.2754; found, 271.2749.



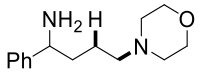
12

1-mesityl-4-morpholinobutan-1-amine, 12:

Prepared using general procedure **C** using: 1-mesitylbut-3-en-1-amine (94 mg, 0.50 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 7.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 12:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **12** (91 mg, 0.33 mmol, 66% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.10 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2H), 4.38 (t, J = 7.5 Hz, 1H), 3.69 (t, J = 4.7 Hz, 4H), 2.39 (m, 10H), 2.33 (dd, J = 8.2, 6.8 Hz, 2H), 2.23 (s, 3H), 1.88 – 1.76 (m, 2H), 1.72 – 1.54 (m, 3H), 1.44 – 1.27 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.77, 136.09 (2C), 135.95, 67.23, 59.13, 53.98, 52.07, 34.48, 24.60, 21.44, 20.88 ppm. IR (salt plate): 3369 (w, br), 3300 (w, br), 2955 (s, br), 2923 (s, br), 2856 (s, br), 2808 (s, br), 1676 (m, br), 1611 (m, s), 1456 (m, br), 1118 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [$M+H^+$] calculated for $C_{17}H_{29}N_2O$, 277.2280; found, 277.2284.



14

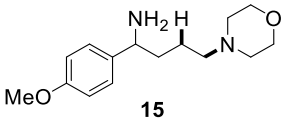
4-morpholino-1-phenylbutan-1-amine, 14:

Prepared using general procedure **C** using: 1-phenylbut-3-en-1-amine (74 mg, 0.50 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 7.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 15:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **14** (110 mg, 0.45 mmol, 90.% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.16 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 3.89 (t, J = 6.9 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 2.38 (br s, 4H), 2.31 (t, J = 7.6 Hz, 2H), 1.77 – 1.60 (m, 2H), 1.58-1.45 (m, 3H), 1.45 – 1.30 (m, 1H) ppm. ^{13}C NMR (125 MHz,

$CDCl_3$): δ 146.68, 128.68, 127.16, 126.51, 67.20, 59.12, 56.48, 53.94, 37.60, 23.80 ppm. IR (salt plate): 3368 (w, br), 3297 (w, br), 3060 (w, s), 3025 (m, s), 2940 (s, br), 2853 (s, s), 2807 (s, s), 1602 (m, s), 1492 (m, s), 1118 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1814.



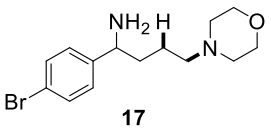
15

1-(4-methoxyphenyl)-4-morpholinobutan-1-amine, 15:

Prepared using general procedure **C** using: 1-(4-methoxyphenyl)but-3-en-1-amine (89 mg, 0.50 mmol, 1.0 equiv) and morpholine (130 μL, 1.5 mmol, 3.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 18:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **15** ($1.0*10^2$ mg, 0.39 mmol, 79% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.25 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.85 (t, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.68 (t, J = 4.7 Hz, 4H), 2.38 (br s, 4H), 2.30 (dd, J = 8.3, 6.9 Hz, 2H), 1.66 (ddt, J = 17.8, 12.9, 7.1 Hz, 2H), 1.59 – 1.44 (m, 3H), 1.43 – 1.30 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.81, 138.77, 127.57, 114.06, 67.24, 59.18, 55.90, 55.56, 53.99, 37.70, 23.88 ppm. IR (salt plate): 3367 (w, br), 3293 (w, br), 2938 (s, br), 2853 (s, br), 2808 (s, s), 2687 (m, s), 1610 (s, s), 1584 (m, s), 1505 (s, s), 1458 (m, br), 1249 (s, br) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1905.



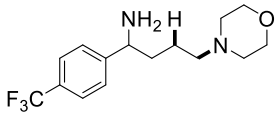
17

1-(4-bromophenyl)-4-morpholinobutan-1-amine, 17:

Prepared using general procedure **C** using: 1-(4-bromophenyl)but-3-en-1-amine (#) (110 mg, 0.50 mmol, 1.0 equiv) and morpholine (130 μL, 1.5 mmol, 3.0 equiv). The reaction was run at 60 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 18:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **17** (140 mg, 0.45 mmol, 90.% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.20 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 3.87 (t, J = 6.8 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 2.37 (m, 4H), 2.30 (t, J = 7.5 Hz, 2H), 1.73 – 1.56 (m, 2H), 1.56 – 1.43 (m, 3H), 1.41 – 1.30 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.56, 131.63, 128.29, 120.68, 67.09, 58.94, 55.82, 53.87, 37.49, 23.58 ppm. IR (salt plate): 3368 (w, br), 3294 (w, br), 2940 (s, br), 2853 (s, s), 2808 (s, s), 2765 (m, s), 1589 (m, s), 1486 (m, s), 1457 (m, s) cm $^{-1}$. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{22}BrN_2O$, 313.0916; found, 313.0915.



18

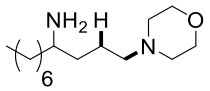
4-morpholino-1-(4-(trifluoromethyl)phenyl)butan-1-amine, 18:

Prepared using general procedure **C** using: 1-(4-(trifluoromethyl)phenyl)but-3-en-1-amine (120 mg, 0.53 mmol, 1.0 equiv) and morpholine (130 μL, 1.5 mmol, 3.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 16:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5%

MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **18** (140 mg, 0.47 mmol, 89% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.51 (5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 3.98 (t, J = 6.8 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 2.38 (br s, 4H), 2.31 (t, J = 7.5 Hz, 2H), 1.76 – 1.61 (m, 2H), 1.52 (m, 3H), 1.42-1.32 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.7, 129.6 (q, J = 32.4 Hz), 126.99, 125.68 (q, $^2J_{CF}$ = 3.8 Hz), 124.48 (q, $^1J_{CF}$ = 272 Hz), 67.22, 59.04, 56.17, 54.00, 37.62, 23.67 ppm. IR (salt plate): 3372 (w, br), 3299 (w, br), 2942 (s, br), 2856 (s, s), 2810 (s, s), 2688 (w, s), 1619 (s, s), 1457 (m, s), 1420 (m, s), 1163 (s, br), 1115 (s, br) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{22}N_2OF_3$, 303.1684; found, 303.1673.



19

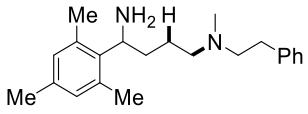
1-morpholinoundecan-4-amine, 19:

Prepared using general procedure **C** using: undec-1-en-4-amine (85 mg, 0.50 mmol, 1.0 equiv) and morpholine (130 μL, 1.5 mmol, 3.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 10:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **19** (94 mg, 0.37 mmol, 73% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.14 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (t, J = 5.1 Hz, 4H), 2.69 (tdd, J = 7.6, 4.7, 4.2 Hz, 1H), 2.44 (br s, 4H), 2.32 (ddt, J = 8.3, 6.4, 1.8 Hz, 2H), 1.65 – 1.33 (m, 6H), 1.33 – 1.20 (m, 10H), 1.11 (br s, 2H), 0.87 (t, J = 6.2 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 67.20, 59.43, 53.99, 51.36, 38.37, 36.09, 32.04, 29.96, 29.51, 26.37, 23.44, 22.85, 14.30 ppm. IR (salt plate): 3373 (w, br), 3292 (w, br), 2956 (m, br), 2924 (m, br), 2853 (m, s), 2807 (m,

s), 1458 (m, br), 1119 (m, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{15}H_{33}N_2O_2$, 257.2593; found, 257.2597.



20

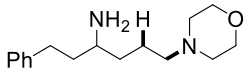
1-mesityl-*N*^{4}-methyl-*N*^{4}-phenethylbutane-1,4-diamine, **20:**

Prepared using general procedure **C** using: 1-mesityl-3-buten-1-amine (95 mg, 0.50 mmol, 1.0 equiv) and *N*-methyl-2-phenylethan-1-amine (510 μL, 3.5 mmol, 7.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 18:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **20** (140 mg, 0.42 mmol, 83% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

Rf=0.28 (10 : 5 : 85 MeOH : sat. NH_4OH : $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 6.81 (s, 2H), 4.37 (t, J = 7.4 Hz, 1H), 2.77 – 2.72 (m, 2H), 2.61 – 2.54 (m, 2H), 2.49 – 2.33 (m, 8H), 2.28 (s, 3H), 2.24 (s, 3H), 1.88 – 1.72 (m, 2H), 1.67 – 1.46 (m, 3H), 1.45 – 1.29 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.39, 138.37, 135.50, 128.52 (2C), 128.16 (2C), 125.75, 59.46, 57.48, 51.75, 42.01, 34.19, 33.68, 25.09, 21.10, 20.52 ppm.

IR (salt plate): 3369 (w, br), 3289 (w, br), 3085 (m, s), 3061 (m, s), 3053 (s, s), 2945 (s, br), 2961 (s, br), 2789 (s, br), 1610 (m, s), 1495 (m, s), 1453 (s, br) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{22}H_{32}N_2$, 325.2644; found, 325.2641.



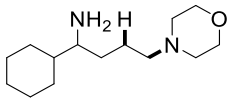
21

6-Morpholino-1-phenylhexan-3-amine, 21:

Prepared using general procedure **C** using: 1-phenylhex-5-en-3-amine (53 mg, 0.30 mmol, 1.0 equiv) and morpholine ($1.0*10^2$ μL, 1.2 mmol, 4.0 equiv) with the exception that the reaction was run at a 1.0 M in DME. The reaction was run at 60 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a >20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 10% MeOH : 2.5% sat. NH_4OH : 87.5% $CHCl_3$ as the eluent) to afford **21** (59 mg, 0.23 mmol, 74% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.10 (1 : 9 MeOH : DCM). ^1H NMR (C_6D_6, 500 MHz): δ 7.15 (m, 5H), 3.62 (t, *J* = 4.75 Hz, 4H), 2.64 (ddd, *J* = 13.6, 9.9, 5.4 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.17 (m, 4H), 2.09 (t, *J* = 7.10 Hz, 2H), 1.59 (dddd, *J* = 14.10, 9.95, 6.60, 4.41 Hz, 1H), 1.35 (m, 4H), 1.11 (m, 1H) 0.74 (br s, 2H) ppm. ^{13}C NMR (C_6D_6 125 MHz): δ 143.50, 129.34, 129.26, 126.63, 67.79, 59.88, 54.79, 51.41, 41.11, 36.96, 33.49, 24.06 ppm. IR (salt plate): 3351 (w, br), 3299 (w, br), 3059 (m, s), 3025 (m, s), 2934 (s, br) 2854 (s, s), 2808 (s, s), 1602 (m, s), 1496 (m, s), 1454 (s, s), 1117 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{16}H_{27}N_2O$: found: 263.2123; found, 263.2128.



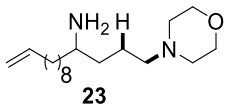
22

1-cyclohexyl-4-morpholinobutan-1-amine, 22:

Prepared using general procedure **C** using: 1-cyclohexylbut-3-en-1-amine (120 mg, 0.76 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 4.6 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 9:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **22** (99 mg, 0.41 mmol, 54% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.15 (15% MeOH : 85% CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (t, J = 4.7 Hz, 4H), 2.49 (dt, J = 8.8, 4.4 Hz, 1H), 2.43 (br s, 4H), 2.38 – 2.27 (m, 2H), 1.79 – 1.56 (m, 6H), 1.52 - 1.41 (m, 2H), 1.28 – 0.93 (m, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 67.10, 59.39, 56.11, 53.91, 43.89, 32.71, 29.90, 27.90, 26.78, 26.70, 26.54, 23.75 ppm. IR (salt plate): 3377 (w, br), 3310 (w, br), 2924 (s, br), 2851 (s, s), 2806 (s, s), 2765 (m, s), 1610 (m, br), 1119 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{29}N_2O$, 241.2280; found, 241.2281.



23

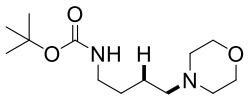
1-morpholinotetradec-13-en-4-amine, 23:

Prepared using a *modified* general procedure **C** using: tetradeca-1,13-dien-4-amine (85 mg, 0.40 mmol, 1.0 equiv) and morpholine (240 μL, 2.8 mmol, 7.0 equiv), 1 M in DME (0.4 mL). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 17:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 3% MeOH : 2.5% sat. NH_4OH : 94.5% $CHCl_3$ as the eluent) to afford **23** (79 mg, 0.27 mmol, 66% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.10 (1 : 9 MeOH : DCM). ^{1}H NMR (C_6D_6, 500 MHz): 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.05 (m, 1H), 5.00 (m, *J* = 10.2, 1.1 Hz, 1H), 3.63 (t, J = 5.2, 4.4 Hz, 4H), 2.55 (tt, J = 7.7,

4.1 Hz, 1H), 2.21 (t, J = 4.1 Hz, 4H), 2.15 (t, J = 7.1 Hz, 2H), 2.00 (qt, J = 7.3, 7.1, 6.8, 1.3 Hz, 2H), 1.52 (m, 1H), 1.46 – 1.10 (m, 17H), 0.73 (br s, 2H) ppm. ^{13}C NMR (C_6D_6 125 MHz): δ 139.81, 115.14, 67.82, 60.03, 54.84, 52.10, 39.67, 37.03, 34.81, 30.90, 30.70, 30.53, 30.14, 29.94, 27.23, 24.25 ppm. IR (salt plate): 3375 (w, br), 3296 (w, br), 3075 (w, br), 2925 (s, br), 2853 (s, s), 2808 (m, s), 1640 (w, s), 1119 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{18}H_{37}N_2O$: 297.2906; found, 297.2911.



25

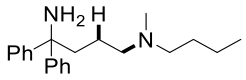
***tert*-butyl (4-morpholinobutyl)carbamate, 25:**

$[Rh(COD)Cl]_2$ (6.2 mg, 0.013 mmol, 2.5 mol %), dppp (10. mg, 0.025 mmol, 5.0 mol %), silver tetrafluoroborate (4.9 mg, 0.025 mmol, 5.0 mol %), DME (330 μL) and homoallyl amine (46,μL 0.49 mmol, 1.0 equiv) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (220 μL, 2.5 mmol, 5.0 equiv). The resulting solution was sealed with-Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 80 °C. After 48 h, the reaction vial was cooled to room temperature.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The vial was opened to air and di-tert-butyl dicarbonate (547 μL, 2.5 mmol, 5 equiv) was added dropwise while vigorous bubbling occurred. The mixture was stirred at room temperature for 15 minutes, excess solvent was removed *en vacuo*, and the dark brown oil was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and 1% MeOH : 5% sat. NH_4OH : 94% $CHCl_3$ as the eluent) to afford **25** ($1.0*10^2$ mg, 0.40 mmol, 83% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

Rf = 0.17 (1 : 5 : 94 MeOH : sat. NH_4OH : $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.31 (s, 1H), 3.73 (t, J = 4.7 Hz, 4H), 3.13 (d, J = 6.7 Hz, 2H), 2.44 (br s, 4H), 2.39 – 2.31 (m, 2H), 1.59 – 1.51 (m, 4H), 1.45 (s, 9H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ 155.92, 78.13, 66.96, 58.52, 53.93, 40.74, 28.57, 28.09, 24.15. IR (salt plate): 3435 (w, br), 3355 (m, br), 3237 (w, br), 2968 (s, br),

2934 (s, br), 2858 (m, s), 2810 (m, s), 2280 (m, s), 1715 (s, br), 1508 (s, br), 1119 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{13}H_{26}N_2O_3$, 259.2022; found, 259.2021.



N^4-butyl-N^4-methyl-1,1-diphenylbutane-1,4-diamine

Prepared using general procedure **A** using: 1,1-diphenylbut-3-en-1-amine (22 mg, 0.097 mmol, 1.0 equiv) and N-methyl-1-butylamine (120 μL, 1.0 mmol, 10. equiv). The reaction was run at 100 °C for 96 h in toluene instead of dimethoxyethane.

Analysis of the crude reaction mixture by gas chromatography determined a 8:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 40 mL of silica in a 3 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 5% MeOH : 2.5% sat. NH_4OH : 92.5% $CHCl_3$ as the eluent) to afford diamine (18 mg, 0.059 mmol, 61% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.43 in 20% MeOH/DCM. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.38 (d, J = 7.4 Hz, 4H), 7.13 (t, J = 7.8 Hz, 4H), 7.03 (t, J = 7.0 Hz, 2H), 2.24 – 2.15 (m, 6H), 2.03 (s, 3H), 1.45 – 1.22 (m, 8H), 0.88 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (C_6D_6 125 MHz): δ 150.52, 128.81, 127.69, 126.89, 61.62, 59.07, 58.50, 42.73, 41.16, 30.65, 23.15, 21.55, 14.93 ppm. IR (salt plate): 3371 (w, br), 3303 (w, br), 3085 (w, s), 3058 (m, s), 3023 (m, s), 2955 (s, s), 2932 (s, s), 2861 (m, s), 2787 (m, br), 1598 (m, s), 1492 (m, s), 1446 (s, s) cm^{-1}. HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{21}H_{31}N_2$: 311.2487; found, 311.2487.

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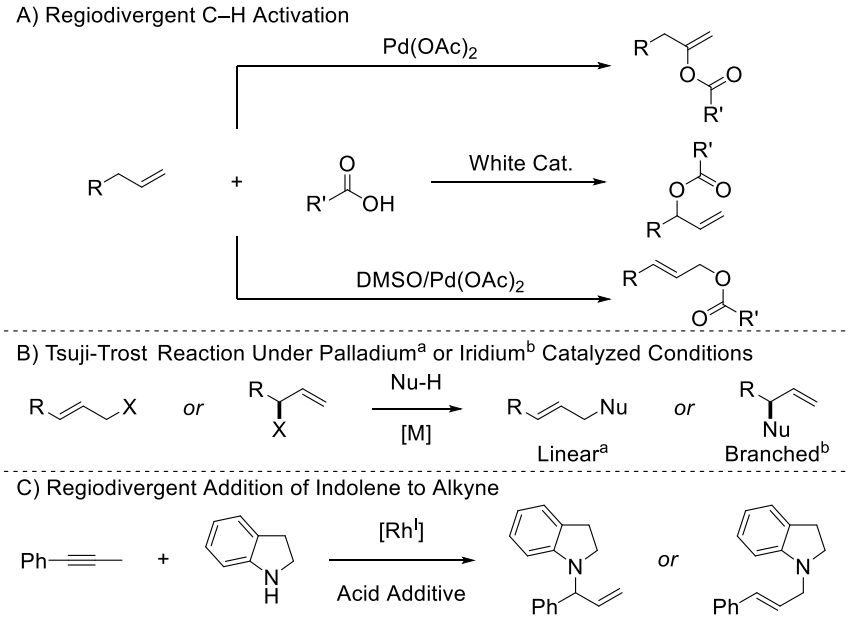
Chapter 4

Intermolecular Regiodivergent Hydroamination of Homoallylic Amines with Aryl Amines to form 1,3- or 1,4-Diamines

4.1 Introduction

Methods for the regiodivergent functionalization of a substrate are powerful approaches to a target molecule and its derivatives. These transformations allows, by varying the choice in catalyst, reaction conditions, etc., access to different regioisomers (formally constitutional isomers) from common starting materials.[1–7] It is worth noting that different mechanisms are often involved in the formation of these different products.[8] Recent advances in this field have featured the branched or linear selective oxidation of an allylic group *via* a palladium catalyzed reaction (Scheme 4.1:A).[9,10] Similarly, the highly branched or linear selective addition of carbon, nitrogen, and oxygen nucleophiles to allylic bromides, acetates, phosphophates, etc. has also been disclosed (Scheme 4.1:B).[11,12] Accessing a π-allyl intermediate, the regiodivergent addition of an amine to an alkyne has also been reported (Scheme 4.1:C).[13]

Scheme 4.1: Significant Reports of Regiodivergent Reactions.

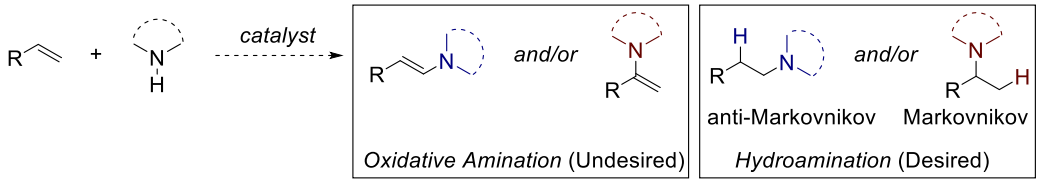


1,3- and 1,4-diamines are common motifs in pharmaceuticals and natural products.[14–16] Hydroamination, the addition of an amine across an unsaturated C–C bond, is an attractive method

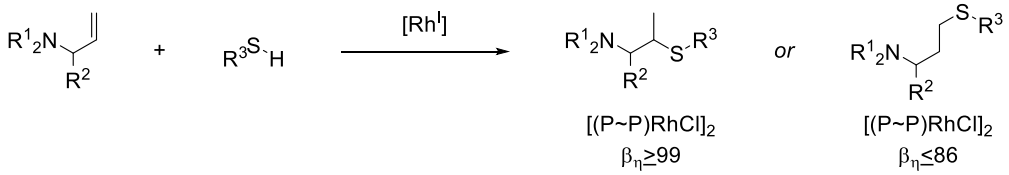
for forming these motifs as it couples two readily accessible functional groups with complete atom economy.[17–21] A variety of transition metal catalysts have been developed to promote intermolecular hydroamination reactions.[22–30]

Despite significant advances, hydroamination reactions commonly suffer from three limitations: reactivity, chemoselectivity, and regioselectivity. First, as the amine is often a better ligand for the metal than the olefin, the reactions generally require a large excess of the alkene coupling partner.[13,31–34] Second, these methods often suffer from competitive formation of both hydro- and oxidative amination products (Scheme 4.2).[32,35] Finally, while hydroamination of unsymmetrical alkenes can afford two possible regioisomers, the reaction is typically substrate controlled (Scheme 4.2). Powerful advances in this methodology can access different regioisomers from a single starting material but are limited in scope.[13,31,36–38] Developing general conditions for the intermolecular regiodivergent hydroamination of alkenes would represent a significant advance in the field. We reasoned that, using methodology developed in our group for the intermolecular regiodivergent hydrothiolation of allylic amines and imines (Scheme 4.3),[8] significant advances for regiodivergent hydroamination could be made.

Scheme 4.2: Products Obtained from Intermolecular Late Transition Metal Catalyzed Hydroamination of Alkenes.



Scheme 4.3: Regiodivergent Intermolecular Hydrothiolation of Allyl Amines and Imines.



Inspired by the above work with aryl thiols, aryl amines were evaluated for their ability to participate in the hydroamination reaction. Aniline was first demonstrated in an intermolecular hydroamination reaction via an oxidative addition pathway in 1988 by Milstein and coworkers.[28] These authors showed iridium catalyzes the addition of anilines to norbornene; this transformation was later rendered asymmetric.[39,40] These reactions were limited to strained alkene coupling

partners to promote olefin insertion. The addition of the N–H bond of indoles to unactivated alkenes, i.e. octene, was reported by Hartwig; this transformation was facilitated by the reversible formation of C/N–bound Ir^{III} intermediates, with olefin insertion occurring selectively into the less stable Ir–N complex to afford the Markovnikov product.[33] Heterocyclic amines (e.g. 2-aminopyidine) have been demonstrated to add across terminal and internal alkenes to afford the Markovnikov hydroamination product.[41] It is proposed that the heterocycle promotes the oxidative addition into the ArN(H)–H. Finally, additional work on the late transition metal-mediated addition of aryl amines to unconjugated alkenes has been reported.[42–47]

While the regiodivergent hydroamination of alkenes with appended Lewis-basic groups is an unsolved challenge in organic chemistry,[17–21] the results discussed in this document allow for the facile formation of 1,2-; 1,3-; and 1,4-diamines. Consider the example of GSK1018921 (Figure 4.1) where seven derivatives of a product are generated from four starting materials. Regioselective and regiodivergent hydroamination is a powerful approach to the synthesis of these diamine motifs.

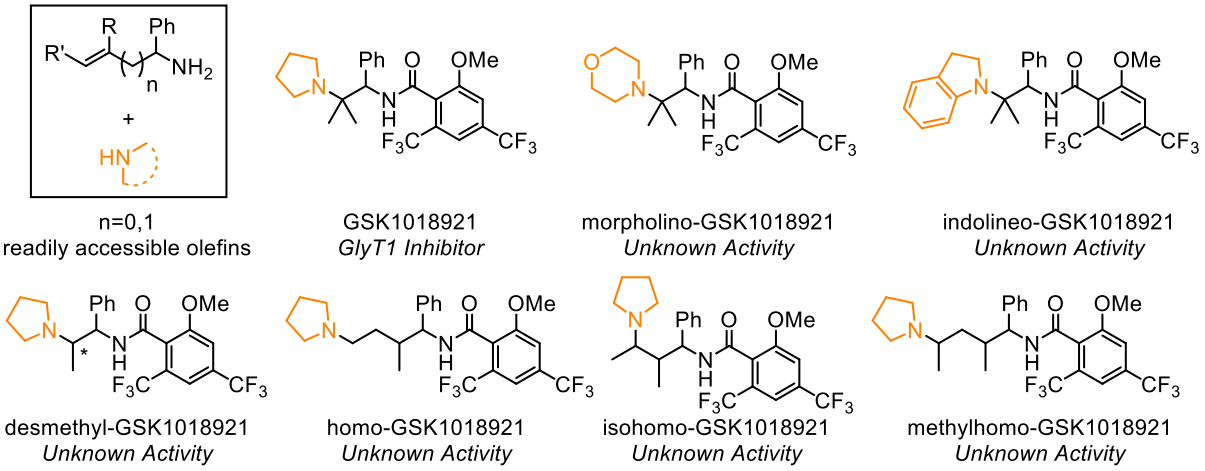


Figure 4.1: GSK1018921 and Several Derivatives that can be Synthesized Utilizing the Methodology Reported Herein.

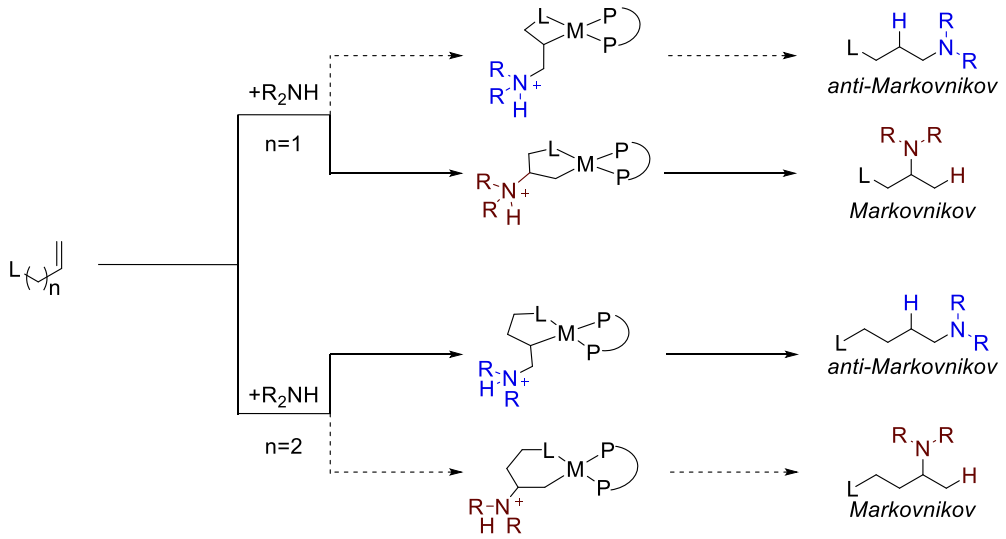
4.2 Regiodivergent Conditions

4.2.1 Rationale

We have previously demonstrated the ability of alkenes with appended Lewis-basic groups to undergo regioselective hydroamination reactions;[48] allylic amines undergo Markovnikov-selective hydroamination[49] and homoallylic amines undergo anti-Markovnikov-selective

hydroamination.[50] However, this work has been inherently limited by the bias of the substrate to form a five-membered metalacyclic intermediate. We sought to expand the scope of this transformation to allow for the selective formation of differently numbered metalacyclic intermediates on the same substrate. This would allow for either Markovnikov or anti-Markovnikov hydroamination to occur on the same substrate. Considering our previous reports,[49,50] this method could be developed on either allylic amines/imines or homoallylic amines (Scheme 4.4).

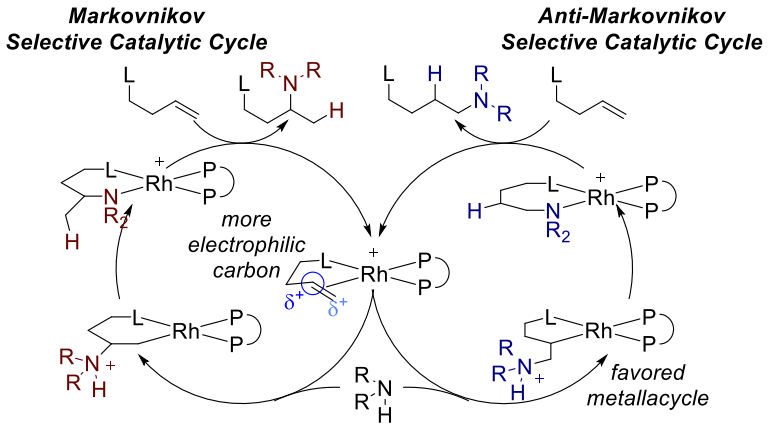
Scheme 4.4: Representative Pathways for the Regiodivergent Hydroamination of Allylic and Homoallylic Lewis-Basic Substrates with Electron Rich Nucleophiles.



Conditions for regiodivergent hydroamination were initially developed on homoallylic amines. While there are reasonability possibilities for the anti-Markovnikov-selective hydroamination of allylic amines (see Chapter 2) the formation of a four-membered metallacycle would likely be too strained while energy differences between five- and six-membered metalacycles can be far less significant.[51] Based on our previous studies, the favored five-membered metallacycle should be formed to give anti-Markonikov products. However, when terminal alkenes are subjected to reaction conditions, there can be both a steric and electronic preference for the formation of the six-membered metallacycle; the metal center is typically larger than the amine nucleophile so there is a steric preference for that to occupy the less hindered position of the alkene. Forming this six-membered metalacyclic intermediate would place the

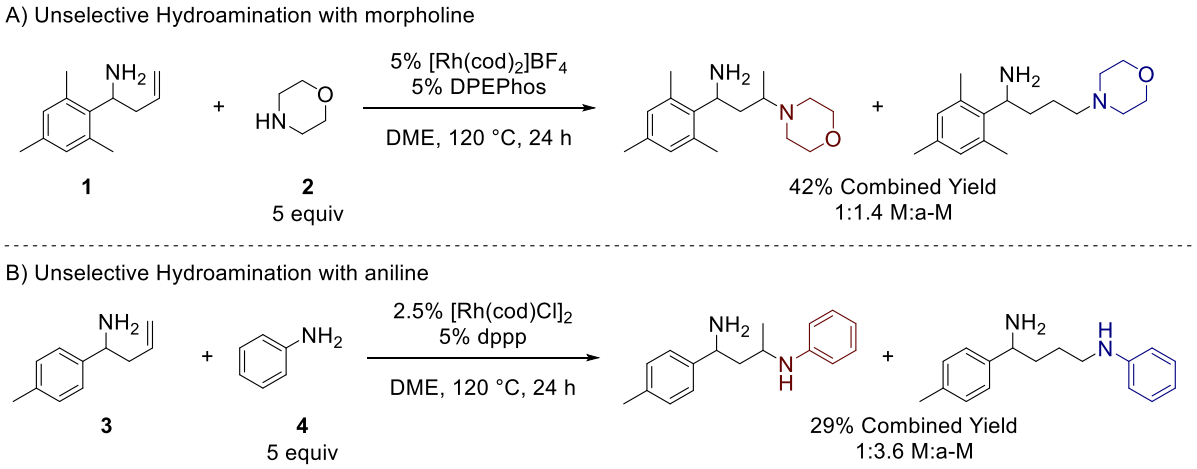
partial positive on the internal position of the alkene during the aminometalation step. The two possible intermediates that can be formed are shown (Scheme 4.5).

Scheme 4.5: Markovnikov and Anti-Markovnikov Selective Catalytic Cycles for Homoallylic Amines Demonstrating a C–C bond Activation Pathway.



Initial results demonstrated that both electron rich and aryl amine nucleophiles can undergo the hydroamination of homoallylic amines in reduced selectivities. When α-mesitylhomoallyl amine is subjected to reaction conditions with morpholine in the presence of a rhodium catalyst, a mixture containing both 1,3- and 1,4-diamine is formed in 42% yield with virtually no selectivity for either product (Scheme 4.6:A). Additionally, when α-tolylhomoallyl amine and aniline react in the presence of a different rhodium catalysts, a mixture of diamine products is also formed (Scheme 4.6:B). Based on previous work by Ms. Jennifer Kennemur and Mr. Gregory Kortman in our group,[8] our explorations began on this class of nucleophile.

Scheme 4.6: Unselective Hydroamination Reactions with Homoallylic Amines.



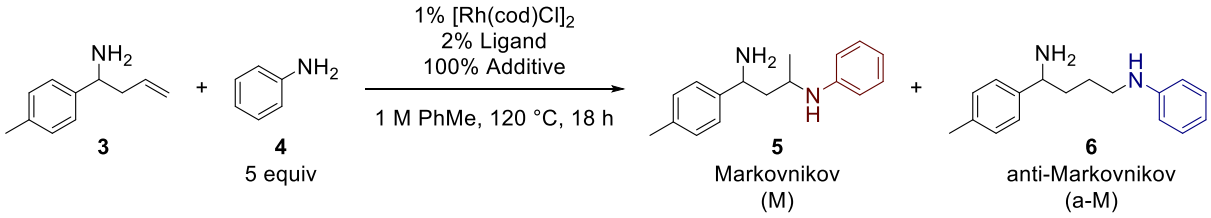
With initial results that showed the hydroamination reaction could proceed in low selectivities, and a mechanistic rational for how either Markovnikov or anti-Markovnikov products could be formed, the reaction was optimized.

4.2.2 Optimization

4.2.2.1 Markovnikov-Selective Hydroamination of Homoallylic Amines

Initial efforts focused on developing a Rh-catalyzed regiodivergent hydroamination reaction. Guided by previous hydroamination reports in the literature,[28,39,40] a variety of neutral Rh^{I} catalysts were investigated. Excitingly, the combination of $[Rh(cod)Cl]_2$ and DPEPhos led to a 4% yield of the desired product **5** in 5.6:1 M:a-M selectivity (Table 4.1, Entry 1). Reasoning that the product may be inhibiting catalyst turnover, a variety of Lewis acidic additives that could bind the formed product were explored. While several lithium (Table 4.1, Entry 2-4) and magnesium salts (Table 4.1, Entry 5-9) significantly improved the yields for this reaction, $MgCl_2$ gave **5** in 75% combined yield and a 7.1:1 ratio of products. When alternative ligands were evaluated, good conversion of the substrate **3** was observed with dppp, dppb, and BINAP, although selectivity for the Markovnikov product was significantly eroded (Table 4.1, Entry 10-14).

Table 4.1: Summarized Optimization for Markovnikov Selective Hydroamination.



Entry	Ligand	Additive	Combined GC Yield (%)	M:a-M
1	DPEphos	none	4	5.6:1
2	DPEphos	LiBr	20	10.0:1
3	DPEphos	LiI	27	7.4:1
4	DPEphos	$LiBF_4$	16	4.4:1
5	DPEphos	MgF_2	2	3.9:1
6	DPEphos	$MgCl_2$	75	7.1:1
7	DPEphos	$MgBr_2$	61	3.0:1
8	DPEphos	MgI_2	5.8	9.5:1
9	DPEphos	$Mg(OTf)_2$	21	4.6:1
10	dppe	$MgCl_2$	<2	n/a
11	dppp	$MgCl_2$	77	1:1.7
12	dppb	$MgCl_2$	73	1.8:1
13	dpppent	$MgCl_2$	23	2.3:1
14	BINAP	$MgCl_2$	48	1:1.8

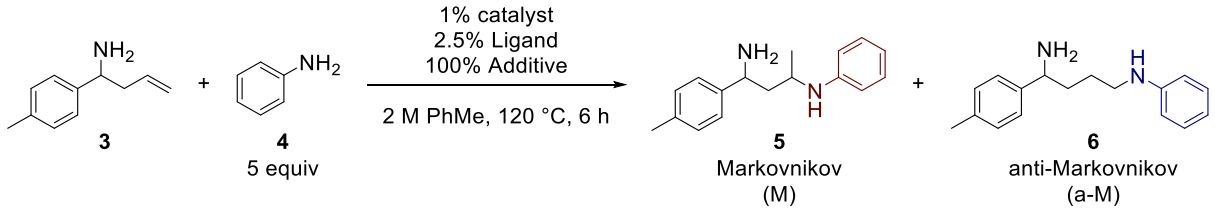
With optimized conditions in hand for the Markovnikov selective hydroamination of homoallylic amines, conditions that allowed for anti-Markovnikov selective hydroamination were elucidated.

4.2.2.2 anti-Markovnikov Selective Hydroamination of Homoallylic Amines

Conditions that allowed for the anti-Markovnikov selective hydroamination of homoallylic amines were examined. A ligand screen demonstrated that the combination of $[Rh(cod)Cl]_2$ and dppp could form the desired 1,4-diamine **6** in 1:1.7 selectivity and 80% combined yield (Table 4.2, Entry 1). However, this selectivity could not be improved by sterically or electronically tuning the ligand. As such, other catalyst systems were explored. A variety of late transition metals have

been reported for hydroamination reactions with aryl amines.[17,18] We reasoned that different metal centers may be able to tune the relative energies between five- and six-membered metalacycles. An $[Ir(cod)Cl]_2$/BINAP system led to a dramatic improvement in both yields and selectivites (Table 4.2: Entry 3). Adding lithium salts (particularly LiI) to the reaction further improved the efficiency for formation of the 1,4-product **6** (Table 4.2, Entry 7). Unfortunately, while exploring the ability of an Ir^I system to mediate the reaction, DPEphos, dppe, dppp, dppb, dpppent, and dppBz were not observed to be effective ligands (Table 4.2: Entries 9-14). While the role of these additives and catalyst in improved selectivity is currently under investigation, we tentatively hypothesize that the Ir-catalyzed conditions can access a later transition state to enhance the selectivity involved in selecting the five-membered metalacycle. (Scheme 4.5).

Table 4.2: Summarized Optimization for the Anti-Markovnikov Selective Hydroamination of a α-Substituted Homoallylic Amine and Aniline.



Entry	[M]	Ligand	Additive	Combined GC Yield (%)	M:a-M
1	$[Rh(cod)Cl]_2$	dppp	none	80	1:1.7
2	$[Ir(cod)Cl]_2$	dppp	none	3	1:3.0
3	$[Ir(cod)Cl]_2$	BINAP	none	62	1:4.5
4	$[Ir(cod)Cl]_2$	BINAP	LiF	60	1:4.1
5	$[Ir(cod)Cl]_2$	BINAP	LiCl	55	1:4.5
6	$[Ir(cod)Cl]_2$	BINAP	LiBr	65	1:5.3
7	$[Ir(cod)Cl]_2$	BINAP	LiI	64	1:11
8	$[Ir(cod)Cl]_2$	BINAP	CsI	49	1:5.1
9	$[Ir(cod)Cl]_2$	DPEphos	LiI	1	1:1.6
10	$[Ir(cod)Cl]_2$	dppe	LiI	<2	n/a
11	$[Ir(cod)Cl]_2$	dppp	LiI	<2	n/a
12	$[Ir(cod)Cl]_2$	dppb	LiI	<2	n/a
13	$[Ir(cod)Cl]_2$	dpppent	LiI	2.0	10.0:1
14	$[Ir(cod)Cl]_2$	dppBz	LiI	<2	n/a

After finding optimized conditions for the regiodivergent hydroamination of homoallylic amines to selectively form either 1,3- or 1,4-diamines, the scope of the transformation was evaluated.[52]

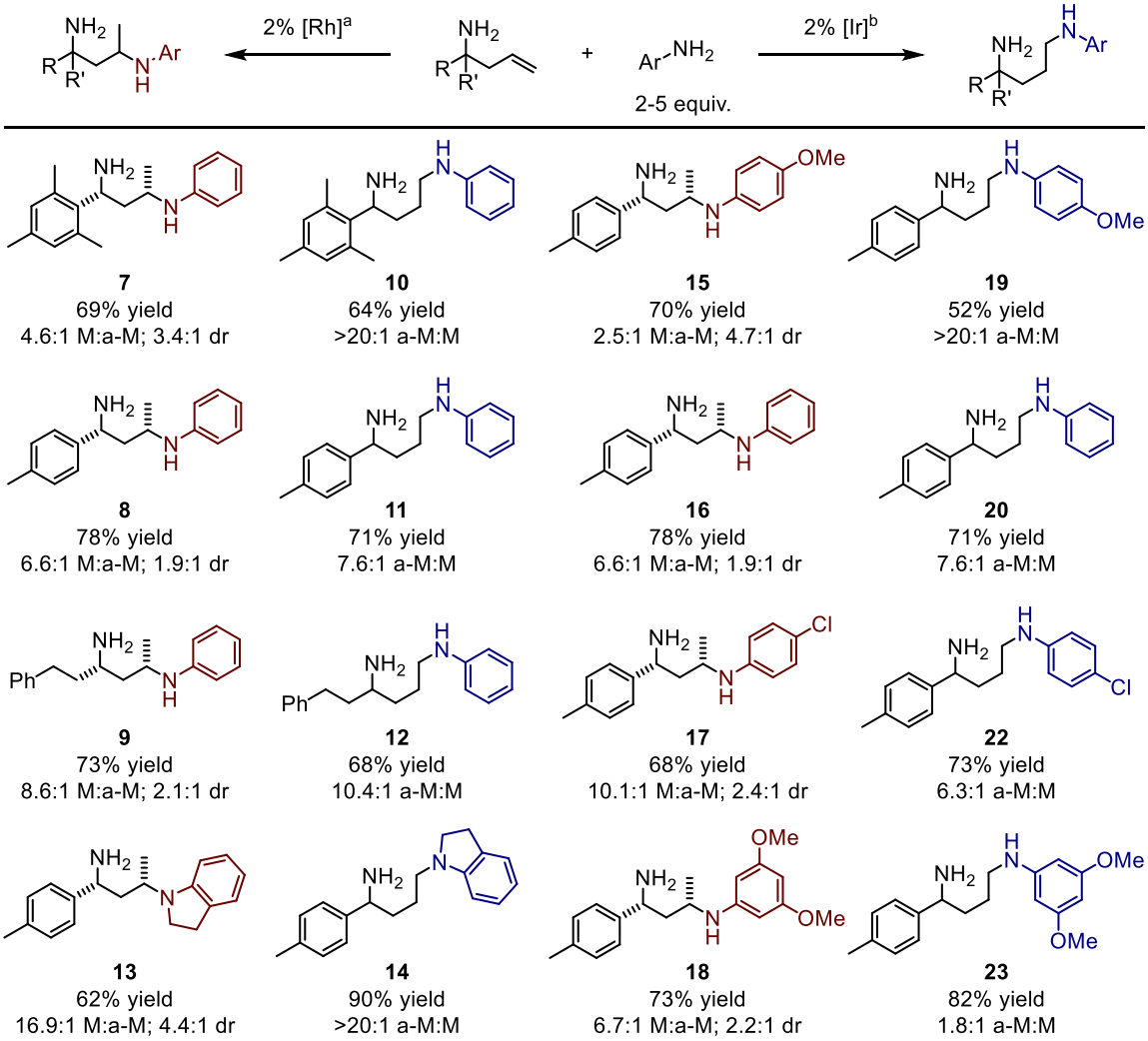
4.3 Markovnikov and anti-Markovnikov Selective Conditions

4.3.1 Scope

After arriving at optimized conditions for both the Markovnikov and anti-Markovnikov selective hydroamination of homoallylic amines, a variety of 1,3- and 1,4-diamines were prepared (Table 4.3). Under Markovnikov selective conditions, less sterically hindered substrates led to

higher selectivity for the 1,3-diamine (**7-9**). In contrast, under anti-Markovnikov selective conditions, more sterically encumbered substrates led to greater fidelity for the 1,4-diamine (**10-12**). In both cases, employing the more sterically encumbered indolene (relative to aniline) led to greater selectivity for the desired product (**13** & **14**). A variety of electron rich and electron poor anilines were also subjected to the hydroamination reaction; greater selectivity was observed under Markovnikov conditions with electron poor aryl amines (**15-18**) while greater selectivity was observed under anti-Markovnikov conditions with electron rich aryl amines (**19-23**).

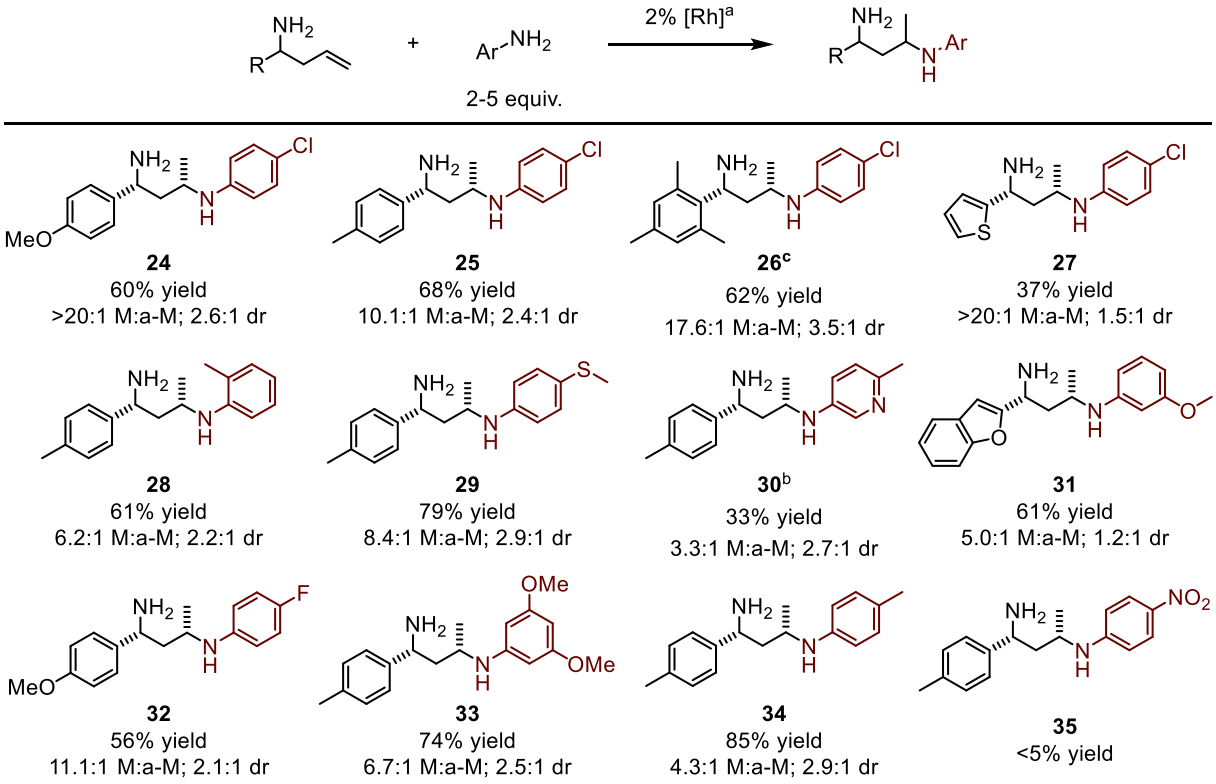
Table 4.3: Comparison of Markovnikov and anti-Markovnikov Selective Conditions for a Variety of Substrates.



[a]1% $[Rh(cod)Cl]_2$, 2% DPEphos, 100% MgCl2, 1 M PhMe, 120 °C, 12-18 h. [b]1% $[Ir(cod)Cl]_2$, 2.5% BINAP, 100% LiI, 2 M PhMe, 120 °C, 6 h.

After comparing a variety of substrates under reaction conditions, the scope of the Markovnikov selective reaction was evaluated. Potentially reactive functional groups, such as aryl chlorides (**24-27**), are well tolerated. Additionally, homoallylic amines bearing bulky α-substituents give the desired 1,3-diamine in excellent selectivity if electron deficient aryl amines are employed (**26**). A variety of heterocycles including thiophenes (**30**), benzofurans (**31**), and pyridines (**30**) are well tolerated under reaction conditions. The sterically encumbered 2-methylaniline (**28**) is a competent nucleophile and both electron rich and electron poor anilines give the desired 1,3-diamine (**28, 31-34**). However, aryl amines bearing significantly electron withdrawing substituents (as demonstrated with 4-nitroaniline) do not give the desired product (**35**).

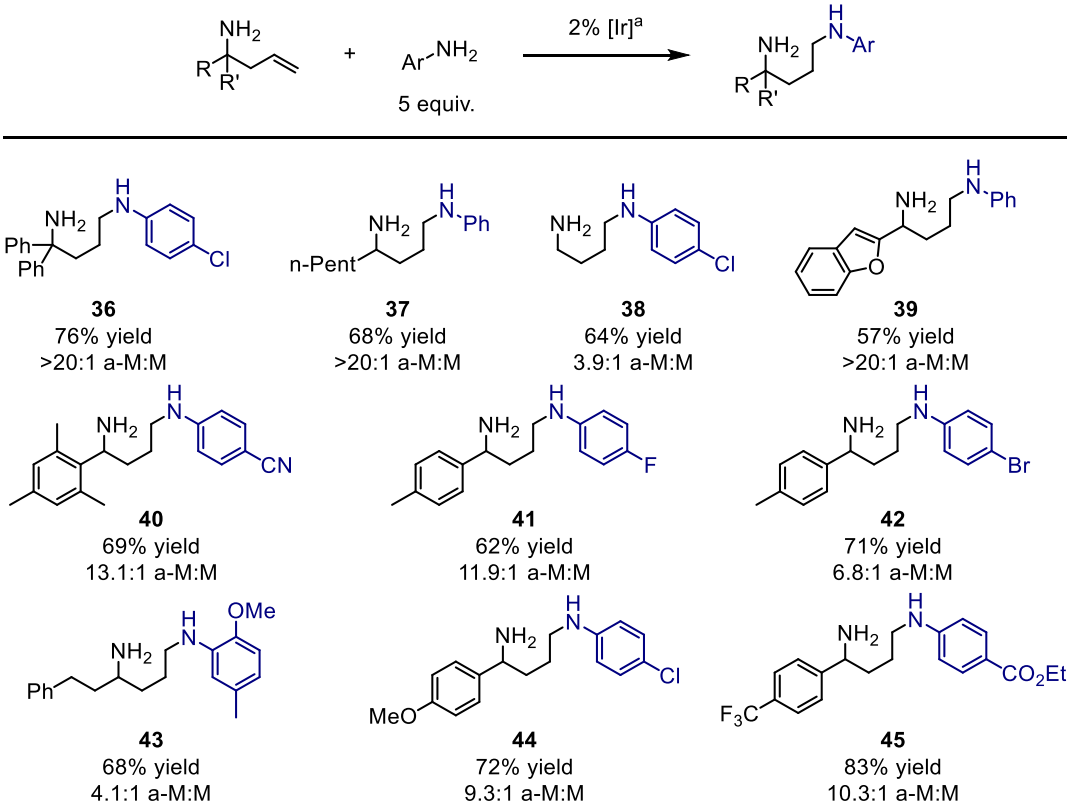
Table 4.4: Representative Scope for the Markovnikov Selective Hydroamination Reaction.



[a]1% [Rh(cod)Cl]$_2$, 2% DPEphos, 100% MgCl2, 1 M PhMe, 120 °C, 12-18 h. [b]3%[Rh(cod)Cl]$_2$, 6% DPEphos, 48 h. [c]The major diastereomer was isolated, cyclized, and characterized by single crystal XRD. The diastereoselectivity for other Markovnikov products is assigned by analogy.

The scope for the anti-Markovnikov selective hydroamination reaction was then examined. Sterically encumbered α,α-disubstituted substrates (**36**), α-substituted substrates (**37**), and homoallyl amine (**38**) were all competent homoallylic amines for the hydroamination reaction. Heterocycle tolerance, including for benzofurans (**39**), was demonstrated. Lewis-basic groups, which could potentially bind out the metal catalyst, could be present under reaction conditions (**40**). Potentially reactive functional groups including aryl chlorides (**42**), aryl bromides (**44**), and esters (**45**) could be employed under reaction conditions. Finally, sterically encumbered nucleophiles gave rise to the desired 1,4-diamine (**43**).

Table 4.5: Representative Scope for the anti-Markovnikov Selective Hydroamination Reaction.



[a]1% [Ir(cod)Cl]$_2$, 2.5% BINAP, 100% LiI, 2 M PhMe, 120 °C, 6 h.

Markovnikov selective conditions give a mixture of cis and trans products. While there is usually limited selectivity for the major diastereomer, the major 1,3-diamine product from the Markovnikov selective hydroamination of α-mesitylhomoallyl amine and *para*-chloroaniline was isolated. After the diastereomers were separated by column chromatography, the diamine was cyclized with CDI, and characterized *via* single crystal X-ray diffraction. Structural determination

was made by Mr. Greg Kortman (Figure 4.2). The diastereoselectivity of the other 1,3-diamines (*vide supra*) were assigned by analogy.

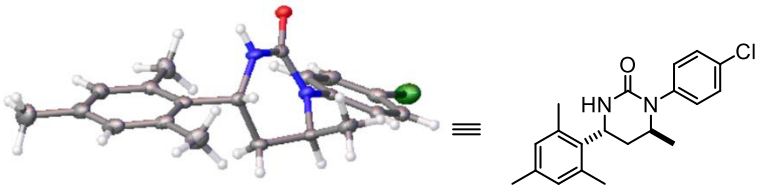


Figure 4.2: Crystal structure of Markovnikov Selective Hydroamination of α-Mesitylhomoallyl Amine and *p*-Chloroaniline After Cyclization with CDI.

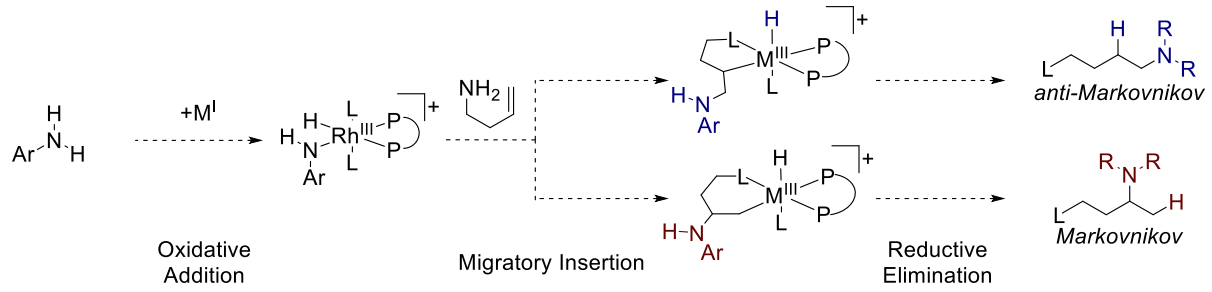
Having elucidated the scope of this transformation and determined the major diastereomer under Markovnikov-selective conditions, preliminary mechanistic studies were carried out to better understand the selectivity of this transformation.

4.4 Mechanistic Studies

4.4.1 Initial Rate Hammett Studies

Aryl amines, in contrast to more electron rich amines, likely proceed through an oxidative addition pathway in the hydroamination reaction.[28] This catalytic cycle involves *i*. oxidative addition into the N–H bond, *ii*. migratory insertion to form the C–N bond and M–C bond, and *iii*. reductive elimination for form a C–H bond and regenerate the catalyst. This pathway is illustrated (Scheme 4.7); it should be noted that this mechanism can be used to access either Markovnikov or anti-Markovnikov products.

Scheme 4.7: Proposed Mechanism for the Regiodivergent Hydroamination of Homoallylic amines.



To test this hypothesis, initial rate Hammett studies were undertaken.[53–55] Under Markovnikov-selective conditions, the initial rate of the reaction first increases and then decreases when moving from electron rich to electron poor aryl amines (Figure 4.3). This is consistent with a change in the turnover-limiting step of the reaction. Further, this suggests that oxidative addition is rate limiting for electron rich aryl amines while the C–N bond forming migratory insertion step is rate determining with more electron deficient anilines. Under anti-Markovnikov-selective conditions (Figure 4.4), electron poor anilines react more rapidly than electron rich; this suggests that oxidative addition is the rate limiting step.[56–58]

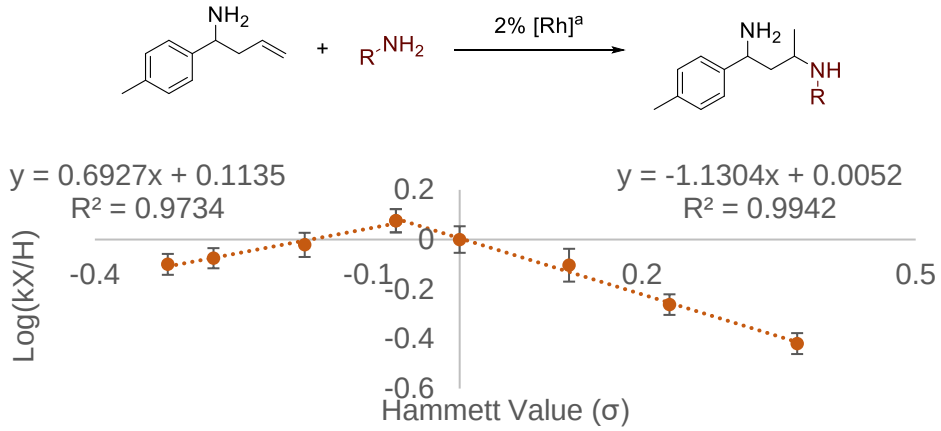


Figure 4.3: Initial Rate Hammett Studies for the Markovnikov Selective Hydroamination of a Homoallyl Amine. [a]1% $[Rh(cod)Cl]_2$, 2% DPEphos, 100% $MgCl_2$, 1 M PhMe, 120 °C, 5 equiv. R-NH_2. R = p-$OBuC_6H_4$, p-$OMeC_6H_4$, p-MeC_6H_4, m-MeC_6H_4, Ph, m-$OMeC_6H_4$, p-ClC_6H_4, and m-ClC_6H_4.

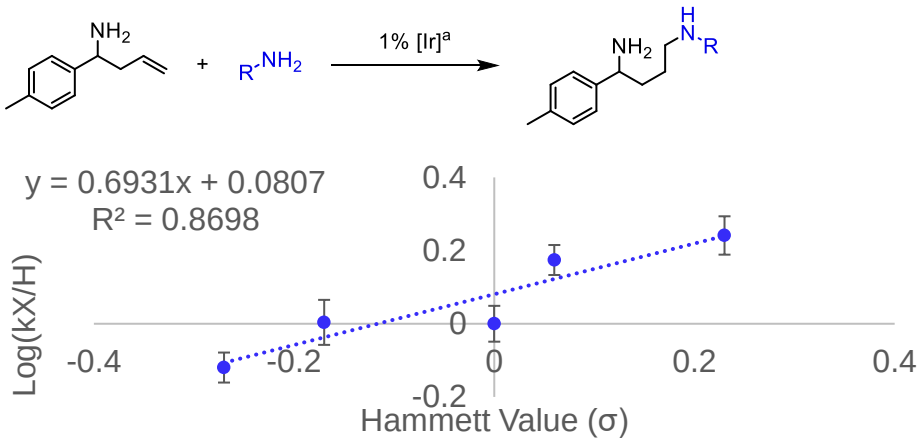


Figure 4.4: Initial Rate Hammett Studies for the Anti-Markovnikov Selective Hydroamination of a Homoallyl Amine. [a]0.5% $[Ir(cod)Cl]_2$, 1.25% BINAP, 100% LiI, 1 M PhMe, 120 °C, 5 equiv. R-NH_2. R = p-$OMeC_6H_4$, p-MeC_6H_4, Ph, p-FC_6H_4, and p-ClC_6H_4.

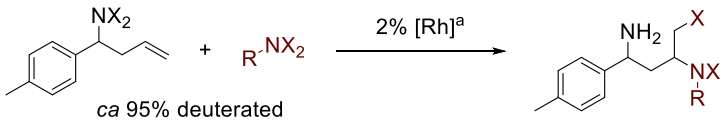
To further support the proposal that hydroamination with aryl amines, in our system, proceeds through an N–H bond activation mechanism, we undertook initial rate Kinetic Isotope Effect (KIE) studies.

4.4.2 Initial Rate Kinetic Isotope Effect Studies

Initial rate KIE studies were undertaken for both Markovnikov and anti-Markovnikov-selective reaction conditions (Table 4.4).[59] Under Markovnikov-selective conditions, both mechanistic regions of the reaction (as defined by the Hammett studies) were evaluated. A primary

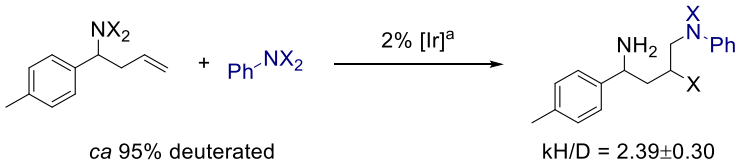
KIE is observed when *para*-methoxyaniline (1.86±0.12), aniline (2.09±0.09), or *para*-chloroaniline (2.13±0.15) are employed. Under anti-Markovnikov-selective conditions, a primary KIE (2.39±0.30) is observed when aniline is used as a nucleophile (Scheme 4.8). As a primary KIE is observed under both 1,3- and 1,4-diamine selective conditions, N–H cleavage occurs at or before the rate limiting step; this supports an N–H activation mechanism.[28,59–62]

Table 4.6: Kinetic Isotope Effect Studies for Markovnikov Selective Conditions. [a]1% $[Rh(cod)Cl]_2$, 2% DPEphos, 100% $MgCl_2$, 1 M PhMe, 120 °C, 5 equiv. R-NH_2.



Entry	R	$k_{H/D}$	Standard Error
1	*p*-OMe	1.86	0.12
2	Ph	2.09	0.09
3	*p*-Cl	2.13	0.15

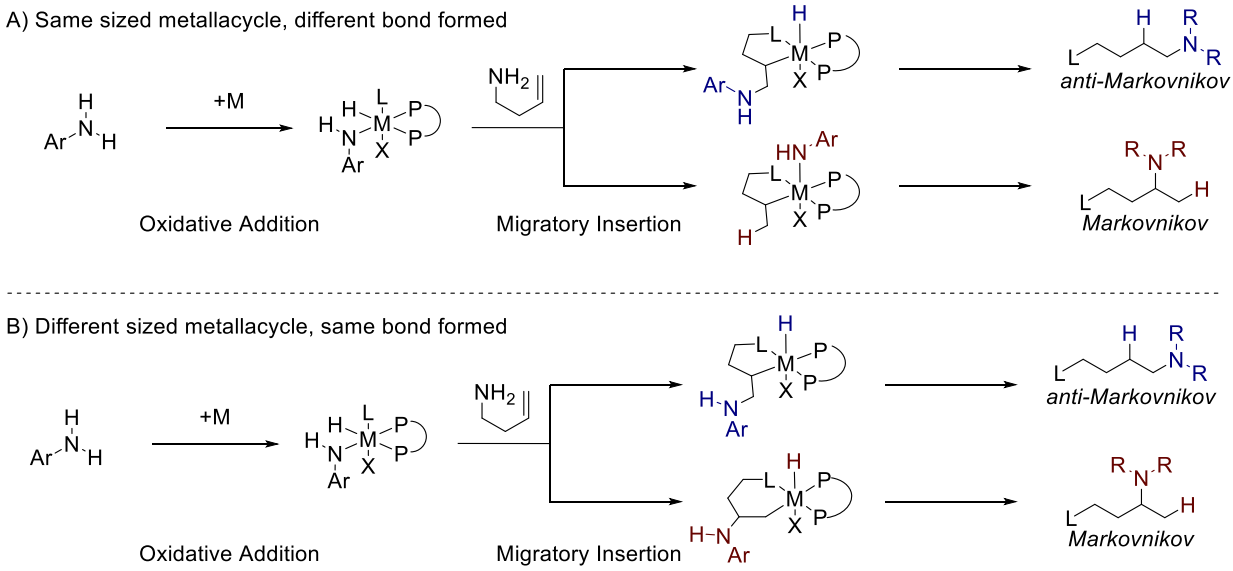
Scheme 4.8: Kinetic Isotope Effect Studies for anti-Markovnikov Selective Conditions. [a]1.0% $[Ir(cod)Cl]_2$, 2.5% BINAP, 100% LiI, 1 M PhMe, 120 °C, 5 equiv. Ph-NH_2.



4.4.3 Rationale for Regioselectivity

We envision two possible pathways for regiodivergent hydroamination. It is possible that (Scheme 4.9:A), during the migratory insertion step, a five membered metalacycle is accessed in both cases but either a C–H or C–N bond is formed. Alternatively (Scheme 4.9:B), either a five- or six-membered metallacycle is formed during the migratory insertion step but, in both cases, a C–N and M–C bond are formed. With these two mechanistic possibilities proposed, we sought to differentiate between them.

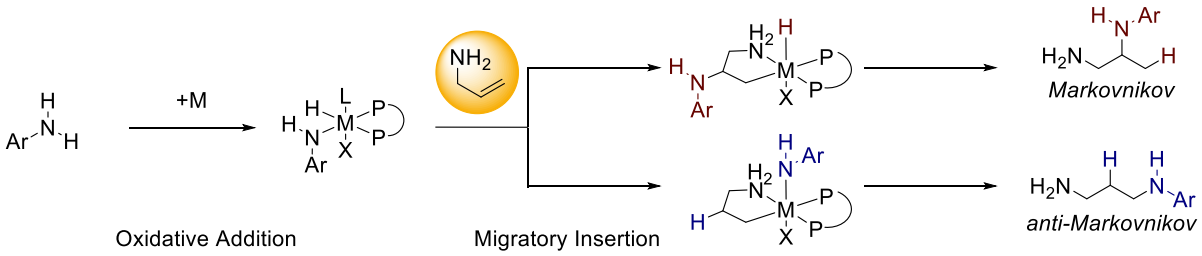
Scheme 4.9: Two Possible Mechanisms for Regiodivergent Hydroamination.



4.4.4 N-*allyl Amine Mechanistic Probe*

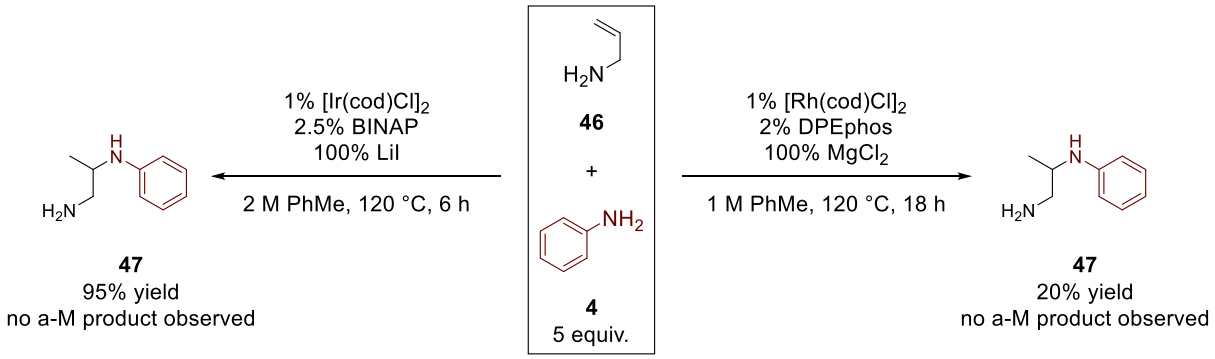
To examine the mechanism by which regiodivergent hydroamination was proceeding, we employed both Markovnikov and anti-Markovnikov selective conditions on allyl amine. It was reasoned that, if a five membered metallacycle was being formed under both 1,3- and 1,4-selective conditions, then it should be possible to observe 1,2-diamines under Markovnikov selective conditions and 1,3-diamines under anti-Markovnikov selective conditions (Scheme 4.10).

Scheme 4.10: Possible Intermediates for the Regiodivergent Hydroamination of Allylic Amines.



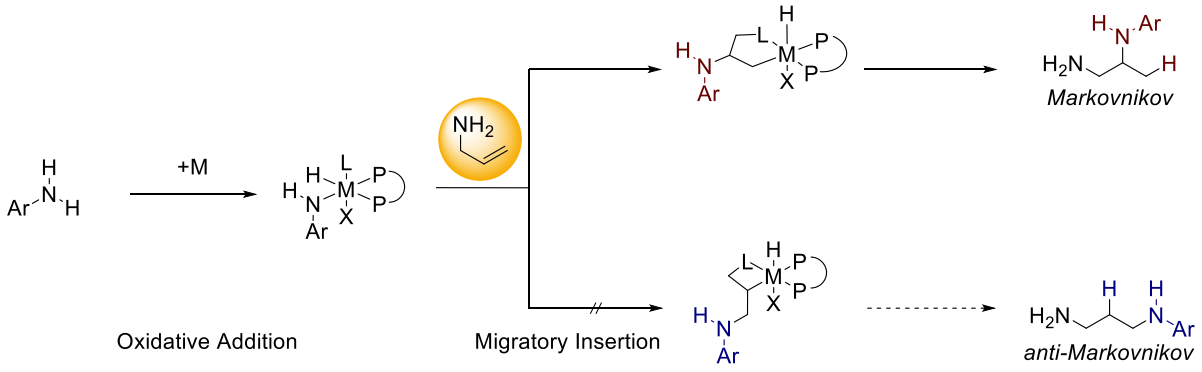
However, only 1,2-diamines are observed under both Rh- and Ir-catalyzed conditions (Scheme 4.11). This does not support the first mechanistic hypothesis (Scheme 4.9:A). It is worth noting that this is in direct contrast to related work for the hydrothiolation of allylic amines and imines.[8]

Scheme 4.11: Products Observed when Allyl Amine and Aniline are Subjected to Rh- or Ir-Catalyzed Conditions for Hydroamination.



Having tentatively discounted the first mechanistic hypothesis for regiodivergent hydroamination, we then explored our alternative mechanistic hypothesis (Scheme 4.9:B). One can imagine that under conditions that allow for regiodivergent hydroamination, differently sized metallacycles are formed under either Markovnikov or anti-Markovnikov selective conditions. With the allyl amine substrate, we might have expected to observe either Markovnikov or anti-Markovnikov products. However, we have previously observed with the regioselective hydroamination of allylic amines (Chapter 2) that four membered metallacycles are likely too strained to form under reaction conditions. As such, the fact that we observed only Markovnikov products when allylic amines are subjected to either Ir- or Rh-catalyzed conditions is likely due to ring strain (Scheme 4.12). This means that differently sized metalacyclic intermediates likely give rise to the regioisomers observed with the hydroamination of homoallylic amines. Given the Hammett, KIE, and model substrate studies discussed above, we have proposed a catalytic cycle for this transformation.

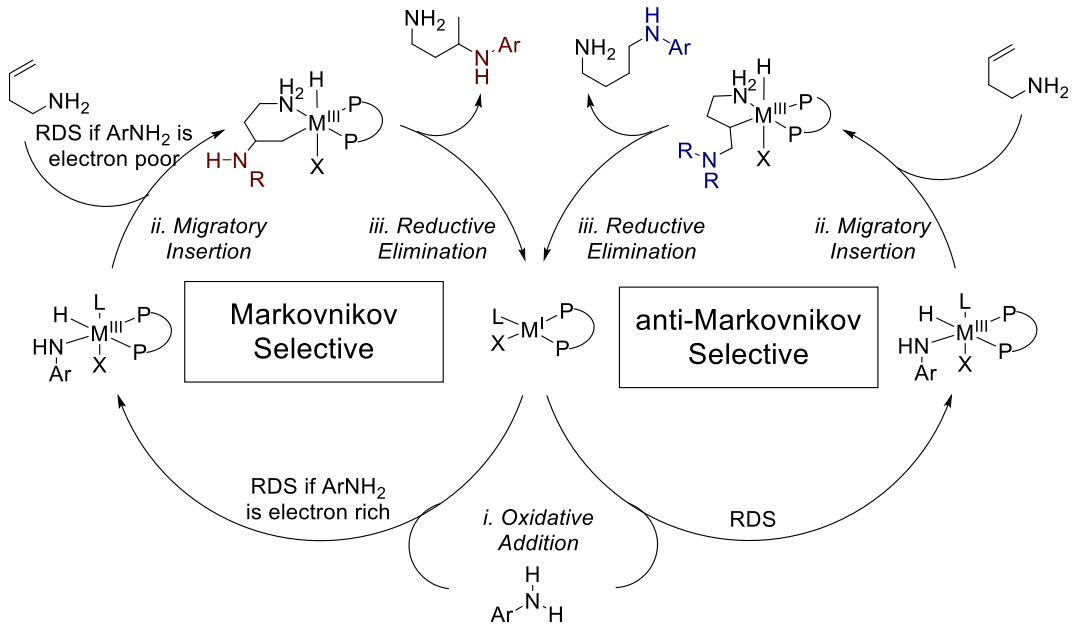
Scheme 4.12: Second Mechanistic Proposal for the Hydroamination of Allylic Amines.



4.5 Proposed Catalytic Cycle

Having considered the mechanistic details discussed above, we propose the following catalytic cycle (Scheme 4.13). Under Markovnikov selective conditions, first, oxidative addition by the neutral M^I complex occurs into the N–H bond of the aryl amine; this is rate limiting if the aryl amine is relatively electron rich. Second, migratory insertion into the alkene of the homoallylic amine occurs to form the desired M–C and N–C bond. This is rate limiting if the aryl amine is relatively electron poor. Third, reductive elimination forms the C–H bond and turns over the catalyst. Under anti-Markovnikov selective conditions, first, oxidative addition occurs into the N–H bond of the aryl amine and this is rate limiting for all aryl amines that were evaluated. Second, migratory insertion forms the desired M–C and N–C bond. Third, reductive elimination forms the C–H bond and turns over the catalyst.

Scheme 4.13: Proposed Catalytic Cycle for the Regiodivergent Hydroamination of Homoallylic Amines.



4.6 Future Directions

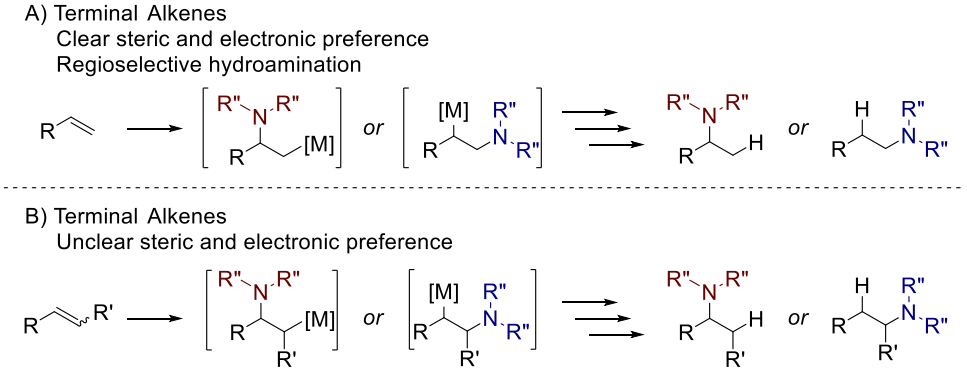
4.6.1 Electron Rich Nucleophiles

Conditions for the hydroamination of homoallylic amines with morpholine in low selectivity have been demonstrated. It seems reasonable that Markovnikov selective conditions could be elucidated. Given that anti-Markovnikov selective hydroamination conditions have already been demonstrated (Chapter 3) developing this method would allow for regiodivergent hydroamination for either electron rich or aryl amines on homoallylic amines.

4.6.2 Internal Alkenes

Both the regiodivergent and regioselective methods for hydroamination discussed in this thesis have featured terminal alkenes (Scheme 4.14:A). The ability to functionalize internal alkenes is an added challenge in the hydroamination literature. Not only are internal alkenes typically more sterically hindered, and as such, less able to bind to a metal center but (unless there is a significant difference been the substituents on the alkene) there is no clear choice of regioisomer when adding an amine across an alkene (Scheme 4.14:B). As such, the intermolecular hydroamination of internal alkenes is an unsolved challenge in transition metal catalysis.[17]

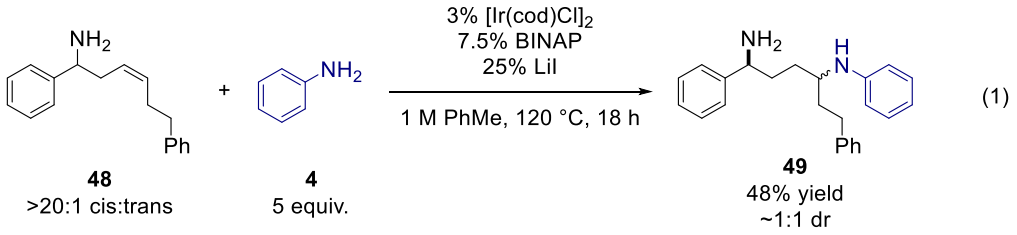
Scheme 4.14: Challenges with the Regioselective Hydroamination of Homoallylic Amines.



We propose that, using allylic or homoallylic Lewis-basic substrates, it should be possible to achieve regioselective hydroamination on substrates with relatively similar substituents on the alkene. Selectivity would be controlled by accessing differently numbered metallacyclic intermediates.

The regioselective hydroamination of internal alkenes to form 1,4-diamines has been observed. The catalyst formed *in situ* from $[Ir(cod)Cl]_2$, BINAP, and LiI catalyzes the

hydroamination reaction with α-phenyl substrate **48** and aniline **4** to form **49** in 48% yield, *ca* 1:1 dr, and no formation of the 1,3-diamine product is observed (Equation 1). Interestingly, omitting the LiI additive leads to only trace product formation under reaction conditions. Alternative ligands are currently being explored to improve the diastereoselectivity.



(1)

The low diastereoselectivity observed for this transformation could be a significant advantage. Essentially, it appears that the α-stereocenter is sufficiently remote from the reactive site of the molecule and does not influence the outcome of the reaction. This suggests that the asymmetric hydroamination of these internal alkenes should be possible and that any issues with a matched/mismatched case between substrate and catalyst would be minimized. If this can be demonstrated, then the next goal of this project will be to synthesize enantioenriched homoallylic amines. By doing this, and then using chiral ligands to catalyze the hydroamination reaction, it will be possible to access all four diastereomers of the 1,4-diamine. Conditions that can achieve this goal are currently under investigation.

The regioselective hydroamination of internal alkenes with various substituents will also be evaluated (Figure 4.5). For example, asymmetric conditions developed for the hydroamination of **48** may also be effective on **49**. The diastereoselective hydroamination of **50** may be far more feasible than **48** due to the proximity of the chiral center. Finally, **51** and **52** would provide interesting insights into the limitations of this directed hydroamination methodology by determining the extent to which, if any, erosion of the regioselectivity and yields is observed.

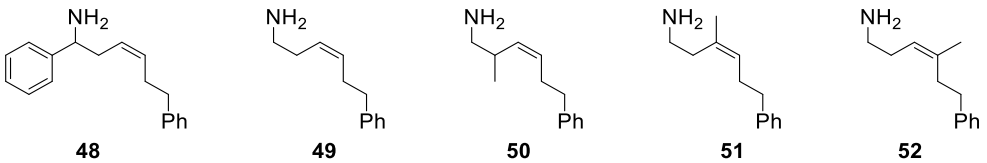


Figure 4.5: Substrates to be Examined Under Regioselective Hydroamination Conditions.

4.7 Conclusion

The ability of aryl amines to undergo the regiodivergent hydroamination of homoallylic amines is disclosed. Markovnikov selective conditions use a Rh^{I} catalyst, DPEphos ligand, and require the stoichiometric addition of $MgCl_2$ to sequester the diamine product. The anti-Markovnikov addition of aryl amines to homoallylic amines is catalyzed by an Ir^{I} catalyst, BINAP ligand, and requires the addition of LiI to obtain the 1,4-diamine product in good yields and selectivities. To better understand the mechanism of the reaction, initial rate Hammett and KIE studies were conducted. Under Markovnikov selective conditions, oxidative addition is rate limiting for electron rich anilines and migratory insertion is rate limiting for electron poor anilines; in both cases, a primary KIE is observed which is consistent with N–H cleavage at or before the rate limiting step. For anti-Markovnikov selective conditions, oxidative addition is rate limiting for all aryl amines. These results are supported by the primary KIEs observed under both 1,3- and 1,4-diamine selective conditions. When allyl amine was evaluated under reaction conditions, the results supported the hypothesis that differently numbered metalacyclic intermediates are formed during the hydroamination of homoallylic amines.

Future work on this project should focus on the regiodivergent addition of electron rich nucleophiles to homoallylic amines and the hydroamination of internal alkenes. The Markovnikov addition of electron rich amines to homoallylic amines appears possible based on the low selectivity observed under unoptimized conditions. Finally, preliminary results demonstrating the regioselective addition of aryl amines to internal alkenes are reported. It is worth noting that developing conditions for regiodivergent and enantioselective hydroamination of internal alkenes would represent a significant advance for both this methodology and the field of intermolecular hydroamination at large.

4.8 Experimental Procedure

General Experimental Procedures:

Unless otherwise specified, all reactions to synthesize homoallylic amines with air sensitive reagents (Grignards, etc.) were carried out in flame-dried glassware under an atmosphere of nitrogen; mildly air sensitive reactions (such as those involving $Ti(OEt)_4$ were not setup in flame-dried glassware. All hydroamination reactions were, and should be, setup under inert atmosphere; while the precatalysts, ligands, amines, and alkenes are all relatively air stable, the active catalyst is not. Nitrogen was dried by passing through drying tube equipped with Drierite. Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level ~ 1.0 ppm) or using standard Schlenk technique. Column chromatography was performed with silica gel from Grace Division Discovery Sciences (35-75 μm mesh); all columns were slurry packed. Analytical thin-layer chromatography (TLC) was performed on precoated glass silica gel plates purchased from EMD Chemicals Inc. and visualized with either short wave (254 nm) ultraviolet light or by staining with $KMnO_4$ and briefly heating. Distillations were performed using a 3 cm short-path column under reduced pressure.

Instrumentation:

^{1}H, ^{13}C, and ^{19}F NMR were recorded using a Varian Unity 400 or 500 MHz (100 or 125 MHz respectively for ^{13}C) or a VXR-500 MHz spectrometer. Spectra were referenced to residual solvent using either $CDCl_3$ (1H NMR: δ7.26 ppm, ^{13}C NMR: δ 77.00 ppm) or C_6D_6 (^{1}H NMR: δ7.15 ppm and ^{13}C NMR: δ 128.60 ppm). ^{19}F NMR are not referenced. Chemical shifts are reported in part per million and the multiplicity is as indicated: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). Coupling constant values are designated by *J* and are reported in Hertz. Integration of the products is provided. Analysis of products and starting materials by Gas Chromatography (GC) where indicated is performed using a Shimadzu GC-2010 Plus Gas Chromatograph equipped with SHRXI-MS-15 m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and Flame Ionization Detector (FID). GC yields are given relative to diphenylmethane as an internal standard unless otherwise indicated. Gas Chromatogrpahy-Mass Spectrometry (GC-MS) analysis is perfrmed using a Shimadzu GC-2010 Plus Gas chromatograph equipped with Shimadzu GCMS-QP2010 SE mass spectrometer. Analyte is separated by way of a SHRXI-5MS- 30 m x 0.25 mm x 0.25 μm column sing helium carrier gas; identification of the

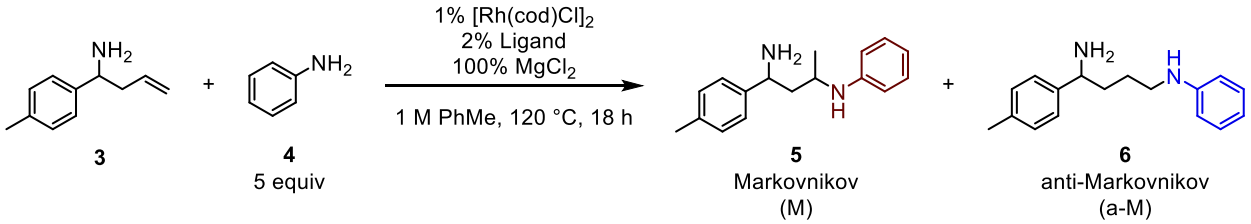
analyte is assisted by electron impact ionization. High Resolution-Mass Spectrometry (HR-MS) is performed in the Department of Chemistry at the University of Illinois at Urbana-Champaign. All air sensitive reactions involving the hydroamination reaction, unless otherwise indicated, were setup with the aid of an MBraun LABmaster SP glove box maintained under nitrogen atmosphere.

Materials:

Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated Stainless Steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted. All amines (excluding allyl amine) were distilled and degassed by the freeze-pump-thaw method, and were stored over 4 Å molecular sieves under an atmosphere of nitrogen in glove box before use. Allylamine was obtained from Aldrich Chemical Co., Inc. and used as received. All liquid aldehydes and amines were freshly distilled prior to use.

Selected Optimization

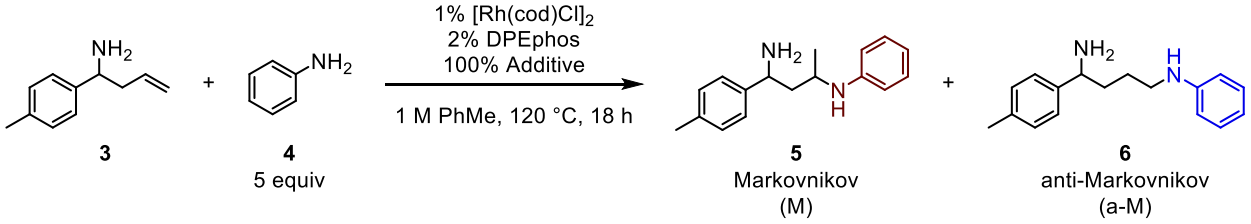
Rhodium Ligand Screens



3 | **4** 5 equiv | **5** Markovnikov (M) | **6** anti-Markovnikov (a-M)

Entry	Ligand	GC Yield (%)	M:a-M
1	DPEphos	75	7.1:1
2	dppe	1	8.8:1
3	dppp	77	0.59:1
4	dppb	73	1.8:1
5	dpppent	23	2.3:1
6	dpph	2.4	6.6:1
7	BINAP	48	0.56:1
8	dppBz	0.1	1.3:1
9	TeaxPhos	2	9.3:1

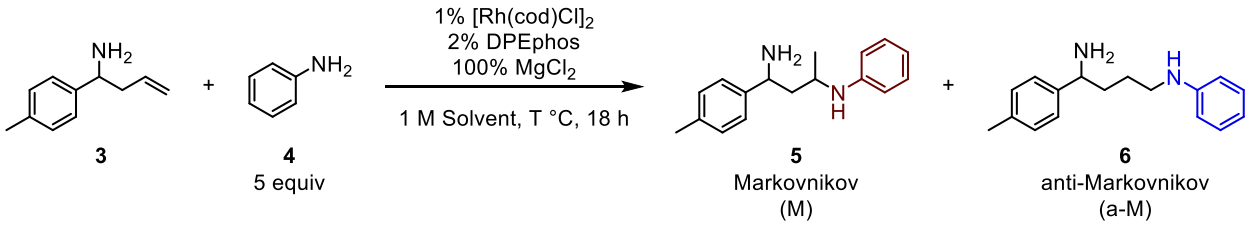
Rhodium Additive Screens



3 | **4** 5 equiv | **5** Markovnikov (M) | **6** anti-Markovnikov (a-M)

Entry	Additive	GC Yield (%)	M:a-M
1	LiF	<2	n/a
2	LiCl	2.2	2.8:1
3	LiBr	20	10.0:1
4	LiI	27	7.4:1
5	LiOAc	2.5	2.8:1
6	$LiBF_4$	16	4.4:1
7	LiOTf	<2	n/a
8	LiTFA	<2	n/a
9	MgF_2	<2	n/a
10	$MgCl_2$	75	7.1:1
11	$MgBr_2$	61	3.0:1
12	MgI_2	5.8	9.5:1
13	$Mg(OAc)_2$	<2	n/a
14	$Mg(OTf)_2$	21	4.6:1
15	NaI	3.5	15:1

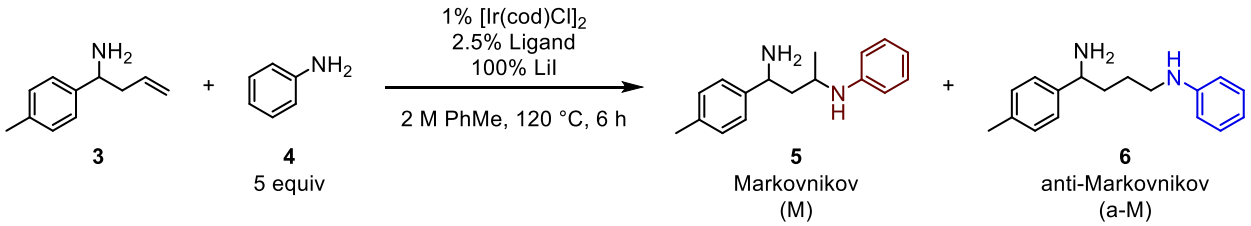
Rhodium Solvent and Temperature Screens



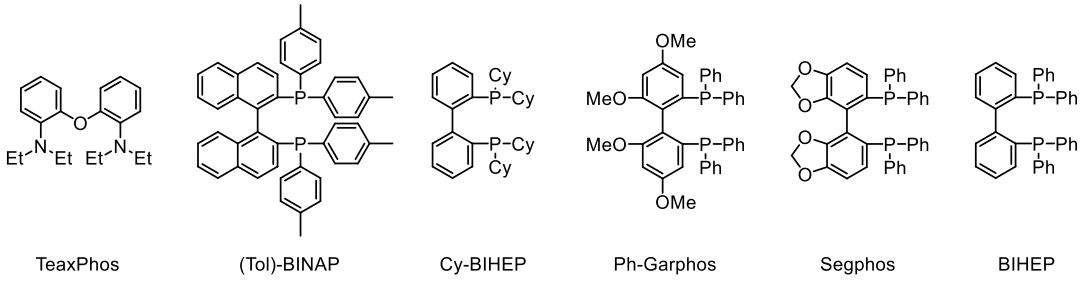
3 | **4** 5 equiv | **5** Markovnikov (M) | **6** anti-Markovnikov (a-M)

Entry	Solvent	Temperature	GC Yield (%)	M:a-M
1	Dioxane	60	<2	n/a
2		80	2	24.5
3		100	29	7.9
4		120	45	4.9
5		140	35	11.1
6	MeCN	60	<2	n/a
7		80	6	4.8
8		100	23	5.4
9		120	21	0.8
10		140	34	0.2
11	THF	60	<2	n/a
12		80	17	6.6
13		100	43	8.4
14		120	62	7.6
15		140	43	12.4
16	PhMe	60	<2	n/a
17		80	20	2.9
18		100	58	3.2
19		120	73	5.0
20		140	51	13.2

Iridium Ligand Screens

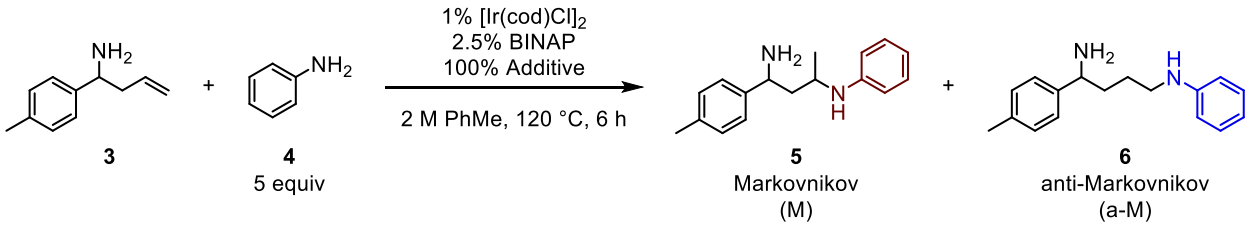


Entry	Ligand	GC Yield (%)	M:a-M
1	DPEphos	<2	n/a
2	dppe	<2	n/a
3	dppp	2	2.0:1
4	dppb	3	27.2:1
5	dpppent	2	17.9:1
6	dpph	2	1.5:1
7	BINAP	64	1:7.6
8	PPh_3	11	3.9:1
9	TeaxPhos	<2	n/a
10	(Tol)-BINAP	63	1:7.5
11	Cy-BIHEP	2	10:1
12	Ph-Garphos	63	1:7.3
13	Segphos	64	1:6.0
14	BIHEP	70	1:6.8



Racemic ligands were employed when screening.

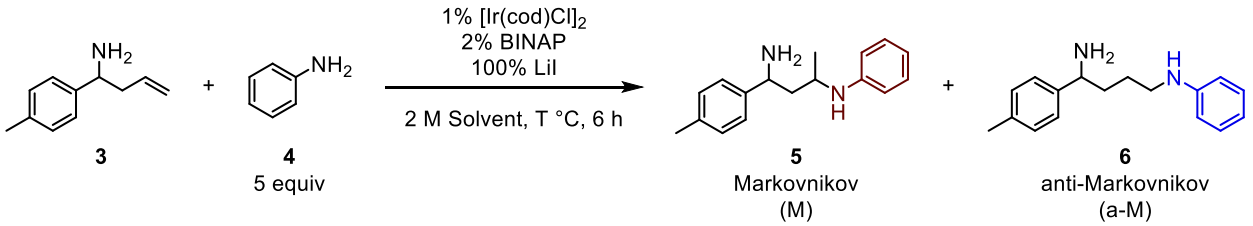
Iridium Additive Screens



3 **4** 5 equiv **5** Markovnikov (M) **6** anti-Markovnikov (a-M)

Entry	Additive	GC Yield (%)	M:a-M
1	None	55	1:4.0
2	LiF	49	1:4.0
3	LiCl	51	1:4.1
4	LiBr	70	1:4.9
5	LiI	75	1:7.6
6	LiOAc	58	1:4.2
7	$LiBF_4$	54	1:2.1
8	LiTFA	67	1:5.1
9	MgF_2	50	1:4.4
10	$MgCl_2$	9	1:1.2
11	$MgBr_2$	24	1:1.4
12	MgI_2	3	1:0.8
13	$Mg(OAc)_2$	45	1:5.0
14	NaCl	57	1:4.2
15	NaI	47	1:17.5

Iridium Solvent and Temperature Screens



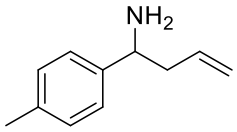
Entry	Solvent	Temperature	GC Yield (%)	M:a-M
1	Dioxane	60	0	0.6
2		80	9	3.8
3		100	73	5.6
4		120	65	8.3
5		140	38	11.0
6	MeCN	60	0	0.6
7		80	0	0.8
8		100	22	4.8
9		120	56	6.7
10		140	38	9.0
11	THF	60	0	0.5
12		80	3	3.8
13		100	64	5.4
14		120	51	9.4
15		140	47	21.7
16	PhMe	60	0	0.6
17		80	1	0.2
18		100	9	4.3
19		120	69	6.5
20		140	45	7.8

Substrate Synthesis

General Procedure A:

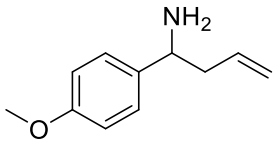
Aldehyde (1.0x mmol, 1.0 equiv), tert-butanesulfinamide (1.1x mmol, 1.1 equiv), titanium ethoxide (1.5x mmol, 1.5 equiv), and THF (1 M relative to aldehyde) were combined in a 100 mL round bottom flask equipped with stir bar. The flask was topped with condenser, placed under N_2, and refluxed overnight. After refluxing, the reaction mixture was cooled to room temperature and quenched with 2-5 mL water. The resulting slurry was stirred for one minute, filtered, and the residue was washed 3 x 50 mL CHCl3. The filtrate was collected, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The crude reaction mixture was used without further purification.

To an oven dried 100 mL Schlenk flask equipped with stir bar was added the crude imine product (1.0x mmol, 1.0 equiv). Dry THF (1 M relative to imine) was added and the Schlenk flask was placed under N2. The reaction mixture was cooled to 0 °C and allylmagnesium chloride (1.1x mmol, 2 M in THF, 1.1 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred for two hours. The reaction mixture was then cooled to 0 °C, quenched with 10 mL methanol, hydrolyzed with aqueous HCl (6.0x mmol, 6 M, 6 equiv), warmed to room temperature, and stirred for one hour. The reaction mixture was then **slowly** basified with 50% NaOH, filtered, and the residue was washed 3 x 50 mL CHCl3. The filtrate was collected, extracted 3 x 100 mL CHCl3, dried with MgSO4, filtered, and the solvent was removed *in vacuo.* The crude amine product was then purified by silica gel to afford the pure homoallyl amine.

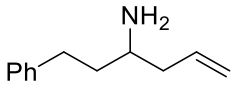


1-(p-tolyl)but-3-en-1-amine. The product was synthesized according to General Procedure A.

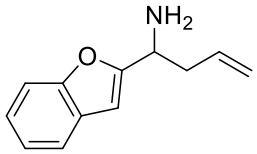
R_f = 0.69 (25:75 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 5.76 (dddd, *J* = 16.7, 10.2, 8.0, 6.3 Hz, 1H), 5.12 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.07 (ddt, *J* = 10.2, 2.1, 1.0 Hz, 1H), 3.96 (dd, *J* = 8.1, 5.3 Hz, 1H), 2.45 (dddt, *J* = 14.6, 6.5, 5.3, 1.4 Hz, 1H), 2.40 – 2.29 (m, 4H), 1.50 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.07, 136.65, 135.75, 129.22, 126.33, 117.63, 55.24, 44.36, 21.19. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C11H16N = 162.1283; found mass = 162.1275.



1-(4-methoxyphenyl)but-3-en-1-amine. The product was synthesized according to General Procedure A. R_f = 0.33 (5:95 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.75 (dddd, *J* = 17.2, 10.2, 8.0, 6.3 Hz, 1H), 5.11 (ddd, *J* = 17.1, 3.3, 1.8 Hz, 1H), 5.07 (ddt, *J* = 10.2, 2.0, 1.0 Hz, 1H), 3.95 (dd, *J* = 8.0, 5.4 Hz, 1H), 3.80 (s, 3H), 2.43 (dddt, *J* = 14.5, 6.6, 5.4, 1.4 Hz, 1H), 2.34 (dtt, *J* = 13.8, 8.0, 1.0 Hz, 1H), 1.51 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.69, 138.18, 135.76, 127.47, 117.62, 113.89, 55.42, 54.92, 44.46. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C11H16NO = 178.1232; found mass = 178.1224.

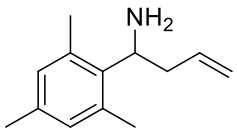


1-phenylhex-5-en-3-amine. The product was synthesized according to General Procedure A. R_f = 0.42 (10:90 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (td, *J* = 7.3, 1.5 Hz, 2H), 7.22 – 7.16 (m, 3H), 5.79 (dddd, *J* = 16.9, 10.5, 8.0, 6.4 Hz, 1H), 5.13 – 5.09 (m, 1H), 5.08 (t, *J* = 1.2 Hz, 1H), 2.83 (tt, *J* = 7.9, 4.7 Hz, 1H), 2.76 (ddd, *J* = 13.6, 10.3, 5.6 Hz, 1H), 2.65 (ddd, *J* = 13.7, 10.2, 6.2 Hz, 1H), 2.28 (dddt, *J* = 13.9, 6.1, 4.6, 1.4 Hz, 1H), 2.04 (dtt, *J* = 13.8, 7.9, 1.1 Hz, 1H), 1.76 (dddd, *J* = 13.6, 10.3, 6.2, 4.9 Hz, 1H), 1.62 (dddd, *J* = 13.5, 10.1, 7.9, 5.6 Hz, 1H), 1.25 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.40, 135.79, 128.52, 128.49, 125.91, 117.59, 50.33, 42.83, 39.56, 32.81. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C12H18N = 176.1439; found mass = 176.1438.

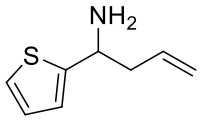


1-(benzofuran-2-yl)but-3-en-1-amine. The product was synthesized according to General Procedure A. R_f = 0.41 (10:90 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.0 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.20 (td, *J* = 7.4, 1.2 Hz, 1H), 6.55 (t, *J* = 1.0 Hz, 1H), 5.81 (dddd, *J* = 17.0, 10.1, 7.5, 6.7 Hz, 1H), 5.28 – 5.08 (m, 2H), 4.14 (ddd, *J* = 7.6, 5.4, 0.9 Hz, 1H), 2.69 (dddt, *J* = 13.6, 6.8, 5.5, 1.4 Hz, 1H), 2.53 (dtt, *J* = 14.0, 7.6, 1.2 Hz, 1H),

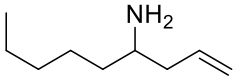
1.60 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.54, 154.84, 134.49, 128.53, 123.84, 122.75, 120.88, 118.46, 111.17, 101.63, 49.78, 40.81. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C12H14NO = 188.1070; found mass = 188.1073.



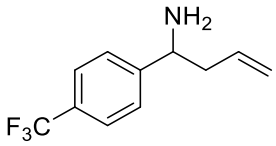
1-mesitylbut-3-en-1-amine. The product was synthesized according to General Procedure A. R_f = 0.38 (5:95 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 2H), 5.77 (dddd, *J* = 17.0, 10.1, 8.1, 6.2 Hz, 1H), 5.12 (dq, *J* = 17.0, 1.6 Hz, 1H), 5.05 (ddt, *J* = 10.2, 2.0, 0.9 Hz, 1H), 4.45 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.63 – 2.35 (m, 8H), 2.24 (s, 3H), 1.51 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.05, 136.55, 136.17, 136.02, 130.42, 116.98, 51.85, 40.99, 21.38, 20.81. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C13H20N = 190.1596; found mass = 190.1597.



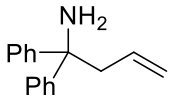
1-(thiophen-2-yl)but-3-en-1-amine. The product was synthesized according to General Procedure A. R_f = 0.43 (10:90 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.95 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.93 (dt, *J* = 3.5, 1.1 Hz, 1H), 5.79 (dddd, *J* = 16.8, 10.2, 7.9, 6.3 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.29 (ddd, *J* = 7.9, 5.2, 0.8 Hz, 1H), 2.58 (dddt, *J* = 14.4, 6.5, 5.2, 1.4 Hz, 1H), 2.43 (dtt, *J* = 13.8, 7.8, 1.1 Hz, 1H), 1.81 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.69, 134.90, 126.70, 123.76, 122.96, 118.35, 51.43, 44.81. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C8H12NS = 154.0690; found mass = 154.0697.



non-1-en-4-amine. The product was synthesized according to General Procedure A. R_f = 0.29 (10:90 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dddd, *J* = 16.9, 10.4, 7.9, 6.4 Hz, 1H), 5.13 – 5.04 (m, 2H), 2.77 (ddd, *J* = 12.1, 5.9, 3.4 Hz, 1H), 2.23 (dddt, *J* = 13.8, 6.0, 4.5, 1.5 Hz, 1H), 1.98 (dtt, *J* = 13.7, 7.9, 1.1 Hz, 1H), 1.46 – 1.21 (m, 10H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.97, 117.18, 50.64, 42.58, 37.62, 31.97, 25.93, 22.66, 14.07. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C9H20N = 142.1596; found mass = 142.1602.

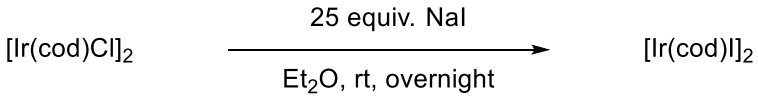


1-(4-(trifluoromethyl)phenyl)but-3-en-1-amine. The product was synthesized according to General Procedure A. R_f = 0.45 (5:95 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 5.73 (dddd, *J* = 16.7, 10.2, 8.0, 6.3 Hz, 1H), 5.15 – 5.09 (m, 2H), 4.07 (dd, *J* = 8.1, 5.2 Hz, 1H), 2.46 (dddt, *J* = 14.2, 6.5, 5.2, 1.4 Hz, 1H), 2.35 (dtt, *J* = 13.8, 8.1, 1.1 Hz, 1H), 1.51 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.97, 134.88, 129.38 (q, *J* = 32.4 Hz), 126.87, 125.48 (q, *J* = 3.8 Hz), 124.22 (q, *J* = 271.4 Hz), 118.37, 55.16, 44.28. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.39. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C11H13NF3 = 216.1000; found mass = 216.0998.



1,1-diphenylbut-3-en-1-amine. To a 100 mL oven dried Schlenk flask under N_2 was added THF (20 mL, 1M) and benzophenone imine (mL, 20 mmol, 1 equiv.). The reaction cooled to 0 °C and allylmagnesium chloride (25 mL, 2.0 M, 50 mmol, 2.5 equiv.) was added dropwise. The mixture was stirred overnight while gradually warming to room temperature. The mixture was cooled 0 °C, quenched with approximately 10 mL MeOH and acidified with approximately 20 mL 6 M HCl. After stirring for 2 h, the reaction mixture was basified with 50% NaOH, extracted with CHCl3, dried with MgSO4, filtered, and solvent was removed by rotary evaporation. Column chromatography (as with General Procedure A) gave the purified product. R_f = 0.52 (5:95 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.3, 1.1 Hz, 4H), 7.30 (t, *J* = 7.7 Hz, 4H), 7.20 (t, *J* = 7.3 Hz, 2H), 5.53 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.20 – 5.06 (m, 2H), 3.02 (dt, *J* = 7.1, 1.2 Hz, 2H), 1.81 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.33, 134.30, 128.24, 126.72, 126.52, 119.29, 60.40, 47.69. HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C16H18N = 224.1439; found mass = 224.1438.

Catalyst Synthesis



[Ir(cod)I]2 was prepared according to modified published procedures. To a 20 mL vial equipped with stir bar was added [Ir(cod)Cl]2 (50.0 mg, 0.074 mmol, 1 equiv.), sodium iodide (279 mg, 1.86 mmol, 25 equiv.), and diethyl ether (5 mL). The heterogeneous dark red mixture was stirred overnight under N_2 and during that time the color changed to bright orange and then to dark purple. The crude mixture was filtered, washed 5 x 5 mL H2O, washed with 2 mL 95% EtOH, dried under suction, and dried under high vacuum. The dark purple powder (52.3 mg, 0.061 mmol) was obtained in 82% yield.

^{1}H NMR (499 MHz, Methylene Chloride-d_2) δ 4.43 (s, 8H), 2.15 (d, J = 38.7 Hz, 8H), 1.29 (d, J = 8.7 Hz, 8H).

Elemental Analysis calculated for $C_{16}H_{24}I_2Ir_2$: C, 22.49; H, 2.83; N, 0.00. Found C, 22.64; H, 2.61; N, 0.08.

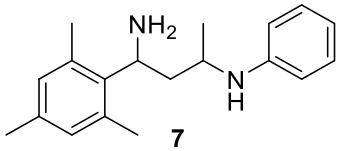
Experimental Procedure

Markovnikov Selective General Procedure B:

To a 4 mL vial equipped with stir bar was added $[Rh(cod)Cl]_2$ (2.47 mg, 5.00 μmol, 1 mol %), DPEphos (5.39 mg, 10.0 μmol, 2 mol %), toluene (500. μL), homoallylic amine (0.5 mmol, 1 equiv) and aryl amine (1.0-2.5 mmol, 2-5 equiv). The 4 mL vial was sealed with Teflon cap, removed from nitrogen filled glove box, and heated to 120 °C for 1 minute with stirring. The reaction mixture was then **cooled to room temperature**, returned to the glove box, uncapped, dry $MgCl_2$ was added (47.6 mg, 0.5 mmol, 1 equiv), the 4 mL vial was resealed with Teflon cap, removed from glove box, and heated to 120 °C for 18 h while stirring.

The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The mixture was then diluted with 50 mL each half-saturated K_2CO_3 (aq) and $CHCl_3$, and the aqueous layer was extracted 3 x 50 mL $CHCl_3$. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (100 mL silica in a 4.5 cm diameter column with 2% sat. NH_4OH : 98% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 2% sat. NH_4OH : 98% $CHCl_3$ to 2% sat. NH_4OH : 5% MeOH : 93% $CHCl_3$ as the eleutant) gave a mixture of Markovnikov and anti-Markovnikov products. Note: while the products were characterized in $CDCl_3$ because it simplified the ^{1}H-NMR spectrum, the absence of chloroform (from column chromatography) was verified by collecting ^{1}H-NMR in benzene-d_6.

Markovnikov Selective Isolated Products



7

1-mesityl-N^3-phenylbutane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (94.7 mg, 0.5 mmol, 1 equiv.) and aryl amine (91.3 μL, 1 mmol, 2 equiv). Analysis of the crude mixture

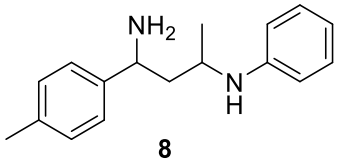
gave the Markovnikov to anti-Markovnikov product as a 4.6:1 mixture and the Markovnikov product in 3.4:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (96.6 mg, 0.342 mmol, 68% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.48 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (ddd, *J* = 8.5, 7.3, 5.4 Hz, 2H), 6.86 (d, *J* = 4.3 Hz, 2H), 6.73 – 6.67 (m, 1H), 6.62 – 6.56 (m, 2H), 4.62 (dd, *J* = 9.0, 4.6 Hz, 1H), 3.73 (tdt, *J* = 7.1, 5.2, 3.6 Hz, 1H), 3.14 (t, *J* = 7.3 Hz, 1H), 2.62 – 2.23 (m, 10H), 2.19 – 2.06 (m, 1H), 1.99 – 1.90 (m, 1H), 1.81 (ddd, *J* = 14.2, 8.1, 4.6 Hz, 1H), 1.25 (dd, *J* = 33.3, 6.2 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.77, 139.07, 138.33, 135.90, 129.26, 127.97, 116.90, 113.12, 48.76, 46.89, 44.22, 21.32, 21.12, 20.63.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C19H27N2 = 283.2174; found mass = 283.2167.



8

N^3-phenyl-1-(p-tolyl)butane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (228 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 6.6:1 mixture and the Markovnikov product in 1.9:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (99.2 mg, 0.390 mmol, 78% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.61 (10:90 MeOH:CH_2Cl_2)

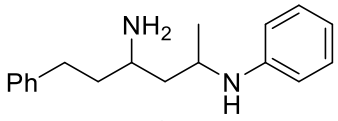
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.11 (m, 6H), 6.71 – 6.62 (m, 1H), 6.53 (dd, *J* = 25.6, 8.1 Hz, 2H), 4.06 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.57 – 3.47 (m, 1H), 2.35 (d, *J* = 5.8 Hz, 3H), 1.93 – 1.41 (m, 5H), 1.18 (dd, *J* = 27.7, 6.2 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.51, 143.60, 136.68, 129.28, 129.24, 126.06, 116.96, 113.21, 53.06, 46.63, 46.09, 21.05, 21.01.

Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.58, 143.87, 136.62, 129.23, 129.19, 126.16, 117.03, 113.39, 54.07, 47.19, 47.10, 21.35, 21.05.

Anti-Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.36, 143.36, 136.66, 129.22, 129.21, 126.19, 117.13, 112.66, 55.85, 43.92, 37.06, 26.62, 21.07.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H23N2 = 255.1861; found mass = 255.1864.



9

N^2,6-diphenylhexane-2,4-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (87.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (137 μL, 1.5 mmol, 3 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as an 8.6:1 mixture and the Markovnikov product in 1.9:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (98.3 mg, 0.366 mmol, 73% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.44 (10:90 MeOH:CH_2Cl_2)

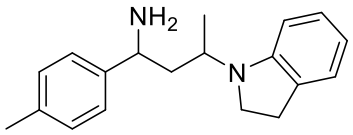
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (q, *J* = 7.3 Hz, 2H), 7.23 – 7.12 (m, 5H), 6.68 (q, *J* = 7.8, 7.3 Hz, 1H), 6.61 (t, *J* = 8.5 Hz, 2H), 3.77 – 3.58 (m, 1H), 3.04 – 2.86 (m, 1H), 2.82 – 2.69 (m, 1H), 2.64 (dtd, *J* = 13.5, 9.8, 6.1 Hz, 1H), 1.88 – 1.47 (m, 7H), 1.19 (d, *J* = 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.62, 141.97, 129.22, 128.34, 128.23, 125.76, 116.82, 113.08, 47.79, 45.79, 45.03, 40.41, 32.48, 21.18.

Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.47, 141.90, 129.19, 128.32, 128.22, 125.74, 117.01, 113.32, 49.55, 45.79, 44.98, 40.98, 32.28, 21.19.

Anti-Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.28, 142.06, 129.14, 128.31, 128.22, 125.72, 117.05, 112.59, 50.60, 43.94, 39.76, 35.35, 29.61, 26.01.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2 = 269.2018; found mass = 269.20131.



13

3-(indolin-1-yl)-1-(*p*-tolyl)butan-1-amine

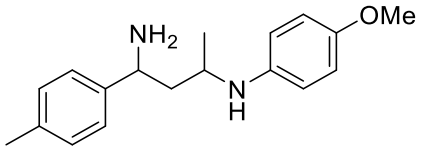
The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (169 μL, 1.5 mmol, 3 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 16.9:1 mixture and the Markovnikov product in 4.4:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (86.0 mg, 0.308 mmol, 62% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.52 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.07 – 6.99 (m, 2H), 6.59 (t, *J* = 7.7 Hz, 1H), 6.30 (d, *J* = 7.9 Hz, 1H), 4.03 (dd, *J* = 8.4, 5.4 Hz, 1H), 3.75 (dp, *J* = 9.0, 6.5 Hz, 1H), 3.41 – 3.26 (m, 2H), 2.99 – 2.92 (m, 2H), 2.35 (s, 3H), 1.93 (ddd, *J* = 14.2, 8.9, 5.4 Hz, 1H), 1.77 (ddd, *J* = 14.0, 8.4, 5.9 Hz, 1H), 1.55 (br s, 2H), 1.09 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.37, 143.65, 136.65, 130.03, 129.26, 127.31, 126.10, 124.39, 116.87, 106.76, 52.94, 47.24, 45.66, 43.60, 28.19, 21.08, 15.16.

HR-MS (EI-TOF) *m/z*: [M+H+] calculated for C19H25N2 = 281.2018; found mass = 281.2006.



15

N^{3}-(4-methoxyphenyl)-1-(*p*-tolyl)butane-1,3-diamine

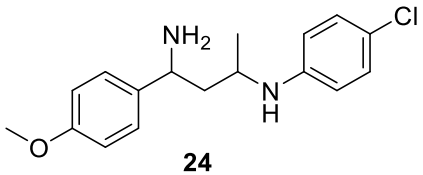
The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (308 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 4.7:1 mixture and the Markovnikov product in 2.5:1 dr.The product was isolated after column chromatography as outlined in General

Procedure B (109.4 mg, 0.384 mmol, 77% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.58 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.14 (m, 4H), 6.82 – 6.73 (m, 2H), 6.58 – 6.49 (m, 2H), 4.10 (dd, *J* = 7.6, 6.0 Hz, 1H), 3.77 (s, 3H), 3.43 (ddt, *J* = 11.8, 8.3, 5.8 Hz, 1H), 2.58 (br s, 3H), 2.37 (d, *J* = 6.7 Hz, 3H), 1.99 – 1.73 (m, 2H), 1.17 (dd, *J* = 27.4, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.96, 143.34, 141.70, 136.72, 129.31, 126.13, 114.93, 114.91, 55.83, 53.15, 47.11, 36.94, 26.70, 21.08.
Minor Diasteromer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.00, 143.48, 141.78, 136.70, 129.27, 126.17, 115.09, 114.83, 55.85, 54.23, 46.45, 36.94, 29.73, 21.41.
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2O = 285.1967; found mass = 285.1956



24

N^3-(4-chlorophenyl)-1-(4-methoxyphenyl)butane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (88.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (191 mg, 1.5 mmol, 3 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a >20:1 mixture and the Markovnikov product in 2.6:1 dr. The product was isolated while following General Procedure B (91.4 mg, 0.300 mmol, 60% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

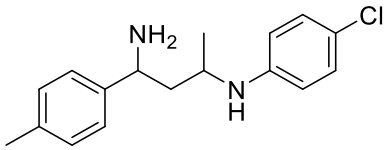
R_f = 0.43 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 18.4, 8.6 Hz, 2H), 7.07 (dd, *J* = 11.7, 8.8 Hz, 2H), 6.87 (dd, *J* = 14.0, 8.7 Hz, 2H), 6.42 (dd, *J* = 28.9, 8.8 Hz, 2H), 4.03 (t, *J* = 6.9 Hz, 1H), 3.81 (d, *J* = 5.1 Hz, 3H), 3.52 – 3.32 (m, 1H), 1.91 – 1.40 (m, 5H), 1.16 (dd, *J* = 31.9, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.61, 146.00, 138.34, 128.94, 127.11, 121.23, 114.15, 113.92, 55.23, 52.72, 46.28, 46.24, 20.70.

Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.56, 146.09, 138.53, 128.96, 127.11, 121.31, 114.27, 113.87, 55.20, 53.50, 47.19, 46.77, 21.11.

HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C17H22N2OCl = 305.1421; found mass = 305.1407.



25

N^3-(4-chlorophenyl)-1-(p-tolyl)butane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (191 mg, 1.5 mmol, 3 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 10.1:1 mixture and the Markovnikov product in 2.4:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (97.1 mg, 0.336 mmol, 67% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

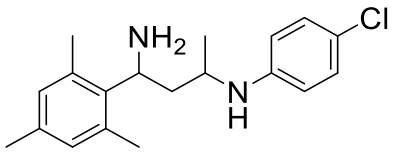
R_f = 0.45 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 4H), 7.07 (dd, *J* = 12.4, 8.8 Hz, 2H), 6.43 (dd, *J* = 29.1, 8.8 Hz, 2H), 4.07 – 3.99 (m, 1H), 3.50 – 3.38 (m, 1H), 2.35 (d, *J* = 5.8 Hz, 3H), 1.91 – 1.69 (m, 2H), 1.57 (br s, 3H), 1.17 (dd, *J* = 29.9, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.08, 143.44, 136.79, 129.32, 129.01, 125.99, 121.35, 114.23, 53.12, 46.41, 46.29, 21.04, 20.79.

Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.15, 143.69, 136.72, 129.28, 129.03, 126.13, 121.45, 114.36, 53.97, 47.37, 46.81, 26.41, 21.20.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H22N2Cl = 289.1472; found mass = 289.1471.



26

N^3-(4-chlorophenyl)-1-mesitylbutane-1,3-diamine

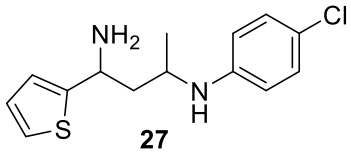
The diamine was synthesized according to General Procedure B using homoallylic amine (94.7 mg, 0.5 mmol, 1 equiv.) and aryl amine (191 mg, 1.5 mmol, 3 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 17.6:1 mixture and the Markovnikov product in 1.5:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (97.3 mg, 0.307 mmol, 61% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.54 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.00 (m, 2H), 6.93 – 6.70 (m, 2H), 6.46 (dd, *J* = 18.7, 8.8 Hz, 2H), 4.56 (dd, *J* = 8.8, 4.9 Hz, 1H), 3.69 – 3.58 (m, 1H), 2.38 (m, 9H), 2.14 – 2.01 (m, 1H), 1.80 (ddd, *J* = 14.2, 7.7, 4.9 Hz, 1H), 1.20 (dd, *J* = 39.1, 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.27, 138.77, 135.94, 128.96, 121.17, 114.32, 114.04, 113.58, 57.72, 48.78, 47.19, 43.79, 20.99, 20.58.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C19H26N2Cl = 317.1785; found mass = 317.1788.



27

N^3-(4-chlorophenyl)-1-(thiophen-2-yl)butane-1,3-diamine

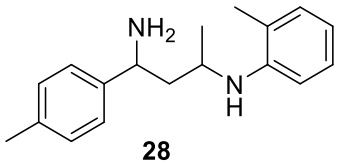
The diamine was synthesized according to General Procedure B using homoallylic amine (76.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (191 mg, 1.5 mmol, 3 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a >20:1 mixture and the Markovnikov product in 1.5:1 dr. The product was isolated after column chromatography as outlined in General

Procedure B (51.4 mg, 0.183 mmol, 37% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.60 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (td, *J* = 5.5, 1.1 Hz, 1H), 7.08 (ddd, *J* = 10.0, 5.4, 2.7 Hz, 2H), 6.98 – 6.93 (m, 1H), 6.90 (dd, *J* = 20.8, 3.7 Hz, 1H), 6.47 (dd, *J* = 8.9, 6.9 Hz, 2H), 4.43 – 4.35 (m, 1H), 3.65 – 3.46 (m, 1H), 2.56 (br s, 2H), 2.00 – 1.82 (m, 2H), 1.26 (s, 1H), 1.19 (dd, *J* = 26.7, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.17, 146.02, 129.07, 126.68, 123.74, 122.83, 121.57, 114.33, 49.16, 47.27, 46.38, 20.81.
Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.17, 146.02, 129.07, 126.68, 123.81, 123.20, 121.68, 114.47, 50.09, 47.22, 46.84, 21.10.
HR-MS (EI-TOF) *m/z*: [M^+] calculated for C14H17N2ClS = 280.08010; found mass = 280.08017.



28

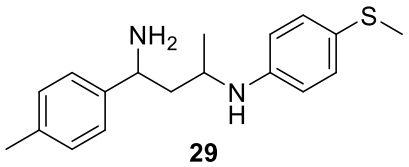
N^3-(o-tolyl)-1-(p-tolyl)butane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (268 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 6.2:1 mixture and the Markovnikov product in 2.2:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (84.2 mg, 0.314 mmol, 63% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.31 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.01 (m, 6H), 6.66 – 6.45 (m, 2H), 4.07 (ddd, *J* = 11.9, 7.7, 6.1 Hz, 1H), 3.66 – 3.51 (m, 1H), 2.35 (d, *J* = 6.9 Hz, 3H), 2.10 (d, *J* = 9.1 Hz, 3H), 2.02 – 1.51 (m, 5H), 1.21 (dd, *J* = 28.7, 6.2 Hz, 3H).

Major Diasteromer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.39, 143.67, 136.70, 130.17, 129.30, 127.03, 126.04, 121.88, 116.27, 110.00, 53.17, 46.64, 45.95, 29.69, 21.05, 17.64.
Minor Diasteromer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.50, 144.01, 136.62, 129.98, 129.25, 127.08, 126.17, 122.13, 116.63, 110.25, 54.14, 47.05, 43.87, 26.64, 21.08, 17.69.
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2 = 269.2018; found mass = 269.2018.



29

N^3-(4-(methylthio)phenyl)-1-(p-tolyl)butane-1,3-diamine

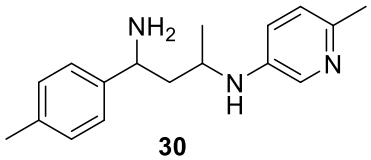
The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (311 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as an 8.4:1 mixture and the Markovnikov product in 2.9:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (117.7 mg, 0.392 mmol, 78% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.31 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.10 (m, 6H), 6.47 (dd, *J* = 27.4, 8.6 Hz, 2H), 4.07 – 4.01 (m, 1H), 3.48 (dq, *J* = 19.5, 6.4 Hz, 1H), 2.41 (d, *J* = 5.3 Hz, 3H), 2.35 (d, *J* = 6.1 Hz, 3H), 1.95 – 1.64 (m, 2H), 1.18 (dd, *J* = 29.7, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.49, 143.36, 136.79, 131.72, 129.36, 126.09, 123.61, 113.81, 53.13, 47.24, 46.25, 21.11, 20.93, 19.35.

Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.56, 143.36, 136.74, 131.65, 129.32, 126.13, 123.71, 113.99, 54.02, 46.75, 46.35, 21.32, 20.93, 19.28.
Anti-Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.32, 143.03, 131.67, 129.27, 126.23, 123.78, 115.06, 113.26, 55.82, 43.89, 36.87, 29.74, 26.48, 21.32.
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2S = 301.1738; found mass = 301.1737.



30

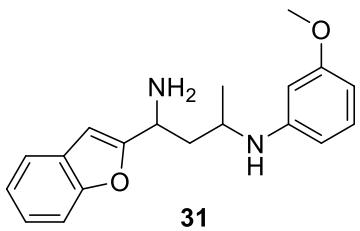
N^3-(6-methylpyridin-3-yl)-1-(p-tolyl)butane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (162 mg, 1.5 mmol, 3 equiv). The product was prepared by following general Procedure B except excess [Rh(cod)Cl]2 (mg, mmol, 3 mol %,) DPEphos (mg, mmol, 6 mol %) was added and the reaction was run for 48 h. Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 3.3:1 mixture and the Markovnikov product in 2.7:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (44.2 mg, 0.164 mmol, 33% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.59 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 9.8, 2.9 Hz, 1H), 7.22 – 7.10 (m, 4H), 6.91 (dd, *J* = 10.7, 8.5 Hz, 1H), 6.72 (ddd, *J* = 25.7, 8.3, 2.9 Hz, 1H), 4.05 (dd, *J* = 7.6, 5.9 Hz, 1H), 3.46 (tq, *J* = 13.7, 6.4 Hz, 1H), 2.42 (d, *J* = 4.9 Hz, 3H), 2.34 (d, *J* = 4.5 Hz, 4H), 1.92 – 1.72 (m, 2H), 1.64 (br s, 2H), 1.17 (dd, *J* = 29.2, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.49, 143.37, 141.23, 136.80, 135.67, 129.35, 125.94, 123.11, 120.25, 53.13, 46.45, 46.21, 23.12, 21.04, 20.79.
Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.62, 143.57, 141.26, 136.76, 135.74, 129.30, 125.98, 123.14, 120.51, 53.97, 47.40, 46.72, 23.14, 21.19, 20.79.
Anti-Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.62, 143.57, 141.97, 134.99, 129.22, 126.19, 126.12, 123.06, 119.73, 55.80, 46.72, 43.89, 36.90, 29.69, 26.47.
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H24N3 = 270.1970; found mass = 270.1971.



31

1-(benzofuran-2-yl)-N^3-(3-methoxyphenyl)butane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (93.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (281 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 5.0:1 mixture and the Markovnikov product in 1.2:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (94.3 mg, 0.304 mmol, 61% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

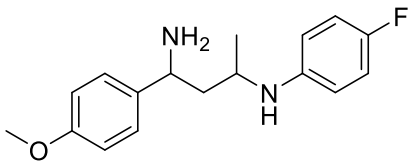
R_f = 0.44 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.5, 3.9 Hz, 1H), 7.44 (dd, *J* = 7.3, 5.1 Hz, 1H), 7.29 – 7.17 (m, 2H), 7.05 (td, *J* = 8.0, 5.6 Hz, 1H), 6.50 (d, *J* = 18.0 Hz, 1H), 6.27 – 6.13 (m, 3H), 4.28 – 4.17 (m, 1H), 3.74 (s, 3H), 3.65 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.22 – 1.48 (m, 4H), 1.24 (dd, *J* = 15.2, 6.3 Hz, 4H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.13, 160.84, 154.65, 148.92, 129.99, 128.35, 123.78, 122.68, 120.73, 111.01, 106.35, 102.40, 101.07, 99.12, 55.02, 48.42, 46.03, 43.24, 21.09.

Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.76, 160.88, 154.64, 148.90, 129.98, 128.34, 123.78, 122.66, 120.78, 111.02, 106.49, 102.32, 101.29, 99.28, 55.02, 47.44, 47.07, 43.36, 21.28.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C19H23N2O2 = 311.1760; found mass = 311.1753.



32

N^3-(4-fluorophenyl)-1-(4-methoxyphenyl)butane-1,3-diamine. The diamine was synthesized according to General Procedure B using homoallylic amine (88.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (237 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 11.1:1 mixture and the Markovnikov product in 2.1:1 dr. The product

was isolated after column chromatography as outlined in General Procedure B (80.8 mg, 0.280 mmol, 56% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

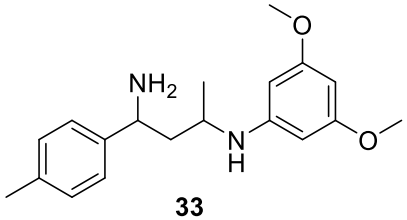
R_f = 0.31 (10:90 MeOH:CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 13.3, 8.6 Hz, 2H), 6.91 – 6.80 (m, 4H), 6.57 – 6.28 (m, 2H), 4.05 (dd, *J* = 7.5, 6.3 Hz, 1H), 3.81 (d, *J* = 5.5 Hz, 3H), 3.45 – 3.33 (m, 1H), 2.30 (br s, 2H), 1.93 – 1.68 (m, 3H), 1.16 (dd, *J* = 30.8, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.72, 155.58 (d, *J* = 234.7 Hz), 143.84 (d, *J* = 1.8 Hz), 138.42, 127.24, 115.63 (d, *J* = 22.2 Hz), 114.18 (d, *J* = 7.3 Hz), 114.01, 55.33, 52.82, 46.90, 46.46, 20.91.

Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.68, 155.64 (d, *J* = 234.5 Hz), 143.94 (d, *J* = 1.8 Hz), 138.58, 127.27, 115.59 (d, *J* = 22.3 Hz), 114.32 (d, *J* = 7.3 Hz), 113.96, 55.30, 53.71, 47.99, 44.58, 21.30.

HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C17H22N2OF = 289.1716; found mass = 289.1730.



33

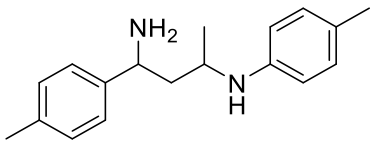
N^3-(3,5-dimethoxyphenyl)-1-(p-tolyl)butane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (383 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 6.7:1 mixture and the Markovnikov product in 2.5:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (120.2 mg, 0.382 mmol, 76% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.46 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.09 (m, 4H), 5.90 – 5.81 (m, 1H), 5.75 (d, *J* = 2.1 Hz, 1H), 5.71 (d, *J* = 2.1 Hz, 1H), 4.04 (dt, *J* = 7.0, 5.1 Hz, 1H), 3.73 (d, *J* = 5.8 Hz, 6H), 3.48 (tq, *J* = 13.2, 7.4, 6.2 Hz, 1H), 2.34 (s, 3H), 1.93 – 1.43 (m, 5H), 1.18 (dd, *J* = 23.8, 6.2 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.73, 149.43, 143.52, 136.67, 129.31, 126.00, 91.85, 89.51, 55.10, 53.03, 47.34, 46.22, 29.69, 21.03.
Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.70, 149.43, 143.52, 136.63, 129.24, 126.06, 93.77, 92.11, 55.15, 54.07, 46.97, 46.55, 29.69, 21.01.
Anti-Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.71, 150.30, 143.32, 136.65, 129.22, 126.19, 91.50, 89.52, 55.83, 55.14, 43.90, 37.03, 26.55, 21.06.
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C19H27N2O2 = 315.2073; found mass = 315.2073.



34

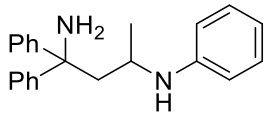
N^3,1-di-*p*-tolylbutane-1,3-diamine
The diamine was synthesized according to General Procedure B using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (268 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 4.3:1 mixture and the Markovnikov product in 2.9:1 dr. The product was isolated after column chromatography as outlined in General Procedure B (118.2 mg, 0.440 mmol, 88% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.54 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.13 (m, 4H), 6.97 (t, *J* = 8.0 Hz, 2H), 6.47 (dd, *J* = 25.9, 8.0 Hz, 2H), 4.07 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.56 – 3.41 (m, 1H), 2.36 (d, *J* = 6.5 Hz, 3H), 2.25 (d, *J* = 5.3 Hz, 3H), 1.95 – 1.69 (m, 2H), 1.17 (dd, *J* = 29.1, 6.3 Hz, 3H).

Major Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.23, 143.50, 136.70, 129.78, 129.31, 126.28, 126.13, 113.55, 53.12, 46.59, 46.39, 26.67, 21.08, 20.38.
Minor Diastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.31, 143.23, 136.66, 129.71, 129.26, 126.23, 126.16, 113.73, 54.16, 47.58, 44.30, 21.40, 21.09, 20.39.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2 = 269.2018; found mass = 269.2020.



46

N^3,1,1-triphenylbutane-1,3-diamine

The diamine was synthesized according to General Procedure B using homoallylic amine (111.7 mg, 0.5 mmol, 1 equiv.) and aryl amine (184 μL, 2.0 mmol, 4 equiv). Analysis of the crude mixture gave the Markovnikov to anti-Markovnikov product as a 1.8:1 mixture. The product was isolated after column chromatography as outlined in General Procedure B (136.7 mg, 0.432 mmol, 86% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.53 (10:90 MeOH:CH_2Cl_2)

Markovnikov Product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 8H), 7.27 – 7.22 (m, 2H), 7.12 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.41 (dd, *J* = 8.4, 1.0 Hz, 2H), 3.29 (h, *J* = 6.3 Hz, 1H), 2.47 (d, *J* = 6.2 Hz, 2H), 1.14 (d, *J* = 6.2 Hz, 3H).
Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.15, 147.72, 147.44, 129.05, 128.26, 128.04, 126.66, 126.51, 126.34, 126.28, 117.28, 113.78, 61.49, 48.44, 46.74, 22.56.

Anti-Markovnikov Product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.1 Hz, 4H), 7.31 (t, *J* = 7.7 Hz, 4H), 7.23 (t, *J* = 7.2 Hz, 2H), 7.17 (dd, *J* = 8.6, 7.2 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 2H), 3.11 (t, *J* = 7.1 Hz, 2H), 2.39 – 2.30 (m, 2H), 1.91 (br s, 3H), 1.63 – 1.51 (m, 2H).

Anti-Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.68, 148.38, 129.24, 128.19, 126.56, 126.42, 117.20, 112.70, 60.96, 44.36, 39.98, 24.49.

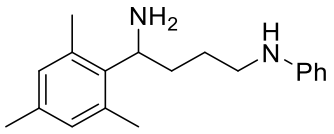
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C22H25N2 = 317.2018; found mass = 317.2003.

Anti-Markovnikov Selective General Procedure C

To a 4 mL vial equipped with stir bar was added $[Ir(cod)Cl]_2$ (3.36 mg, 5.00 μmol, 1 mol %), (±)-BINAP (7.78 mg, 12.5 μmol, 2.5 mol %), lithium iodide (66.9 mg, 0.5 mmol, 1 equiv), toluene (250. μL), homoallylic amine (0.5 mmol, 1 equiv) and aryl amine (2.5 mmol, 5 equiv). The 4 mL vial was sealed with Teflon cap, removed from nitrogen filled glove box, and heated to 120 °C for 6 h while stirring.

The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 15 minutes. The mixture was then diluted with 50 mL each half-saturated K_2CO_3 (aq) and $CHCl_3$, and the aqueous layer was extracted 3 x 50 mL $CHCl_3$. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (100 mL silica in a 4.5 cm diameter column with 2% sat. NH_4OH : 98% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 2% sat. NH_4OH : 98% $CHCl_3$ to 2% sat. NH_4OH : 5% MeOH : 93% $CHCl_3$ as the eleutant) gave a mixture of Markovnikov and anti-Markovnikov products. Note: while the products were characterized in $CDCl_3$ because it simplified the ^{1}H-NMR spectrum, the absence of chloroform (from column chromatography) was verified by collecting ^{1}H-NMR in benzene-d_6.

Anti-Markovnikov Selective Isolated Products



10

1-mesityl-*N*^{4}-phenylbutane-1,4-diamine

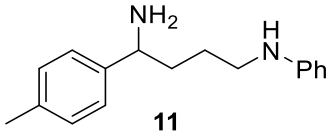
The diamine was synthesized according to General Procedure C using homoallylic amine (94.7 mg, 0.5 mmol, 1 equiv.) and aryl amine (228 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a >20:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (90.1 mg, 0.319 mmol, 64% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.51 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.82 (s, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 7.4 Hz, 2H), 4.41 (t, *J* = 7.5 Hz, 1H), 3.11 (t, *J* = 7.1 Hz, 2H), 2.41 (s, 6H), 2.25 (s, 3H), 2.01 – 1.83 (m, 2H), 1.82 – 1.67 (m, 1H), 1.58 – 1.44 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.35, 138.27, 135.90 (2C), 129.22, 129.18, 117.11, 112.65, 51.79, 44.02, 34.05, 27.42, 21.21, 20.64.

HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C19H27N2 = 283.2174; found mass = 283.2180.



11

N^1-phenyl-4-(*p*-tolyl)butane-1,4-diamine

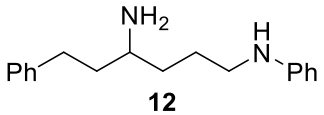
The diamine was synthesized according to General Procedure C using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (228 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 12.3:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (91.1 mg, 0.358 mmol, 72% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.24 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 4H), 6.68 (dd, *J* = 8.1, 6.8 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 2H), 3.89 (t, *J* = 6.9 Hz, 1H), 3.10 (t, *J* = 6.9 Hz, 2H), 2.35 (s, 3H), 1.90 – 1.44 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.36, 143.36, 136.66, 129.22, 129.21, 126.19, 117.13, 112.66, 55.85, 43.92, 37.06, 26.62, 21.07.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H23N2 = 255.1681; found mass = 255.1854.



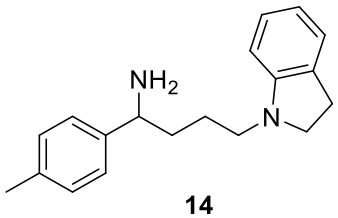
12

N^1,6-diphenylhexane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (87.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (228 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 10.4:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (94.4 mg, 0.352 mmol, 70% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.21 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.19 (dd, *J* = 14.6, 7.2 Hz, 5H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 2H), 3.13 (t, *J* = 7.0 Hz, 2H), 2.77 (dtt, *J* = 15.2, 10.3, 4.4 Hz, 2H), 2.64 (ddd, *J* = 13.6, 10.0, 6.3 Hz, 1H), 1.91 – 1.52 (m, 7H), 1.41 (dddd, *J* = 13.1, 10.2, 7.6, 5.1 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 148.40, 142.21, 129.26, 128.43, 128.36, 125.84, 117.20, 112.72, 50.72, 44.10, 39.99, 35.58, 32.60, 26.18.
HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C18H25N2 = 269.2018; found mass = 269.2023.



14

4-(indolin-1-yl)-1-(*p*-tolyl)butan-1-amine

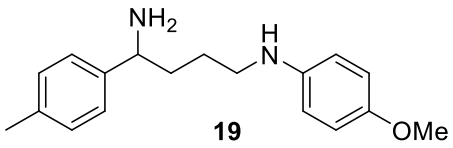
The diamine was synthesized according to General Procedure C using homoallylic amine (111.7 mg, 0.5 mmol, 1 equiv.) and aryl amine (281 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a >20:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (125.8 mg, 0.449 mmol, 90.% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.48 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.09 – 7.03 (m, 2H), 6.64 (td, *J* = 7.4, 1.0 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H), 3.92 (t, *J* = 6.9 Hz, 1H), 3.29 (t, *J* = 8.3 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.95 (t, *J* = 8.3 Hz, 2H), 2.36 (s, 3H), 1.89 – 1.61 (m, 4H), 1.54 (br s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.65, 143.46, 136.56, 129.94, 129.18, 127.24, 126.21, 124.33, 117.27, 106.79, 55.95, 53.07, 49.24, 37.11, 28.55, 24.54, 21.07.

HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C19H25N2 = 281.2018; found mass = 281.2024.



19

N^1-(4-methoxyphenyl)-4-(*p*-tolyl)butane-1,4-diamine

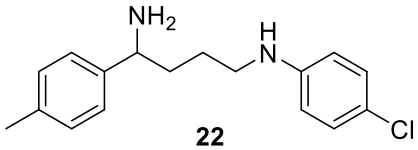
The diamine was synthesized according to General Procedure C using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (308 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a >20:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (73.2 mg, 0.257 mmol, 51% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.38 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.53 (d, *J* = 8.9 Hz, 2H), 3.88 (t, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 3.05 (ddd, *J* = 7.3, 6.6, 1.9 Hz, 2H), 2.34 (s, 3H), 2.17 (br s, 3H), 1.84 – 1.70 (m, 2H), 1.70 – 1.57 (m, 1H), 1.57 – 1.41 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.96, 143.23, 142.66, 136.63, 129.19, 126.18, 114.87, 113.99, 55.84, 55.83, 44.91, 37.01, 26.70, 21.04.

HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C18H25N2O = 285.1967; found mass = 285.1963.



22

N^1-(4-chloroophenyl)-4-(*p*-tolyl)butane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (319 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 6.3:1 mixture. The product was isolated

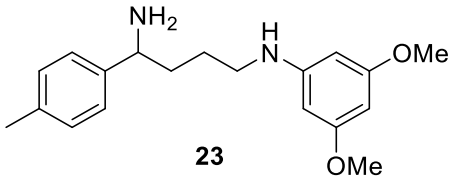
after column chromatography as outlined in General Procedure C (108.3 mg, 0.375 mmol, 75% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.34 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 3.90 (t, *J* = 6.9 Hz, 1H), 3.07 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 1.88 – 1.47 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.86, 143.23, 136.66, 129.19, 128.95, 126.11, 121.54, 113.62, 55.78, 43.97, 36.92, 26.39, 21.02.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H22N2Cl = 289.1472; found mass = 289.1482.



23

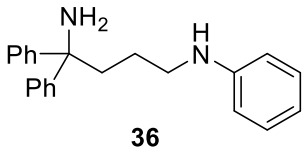
N^1-(3,5-dimethoxyphenyl)-4-(*p*-tolyl)butane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (383 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 1.8:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (128.1 mg, 0.407 mmol, 81% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.44 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 5.89 (t, *J* = 2.2 Hz, 1H), 5.78 (d, *J* = 2.2 Hz, 2H), 3.90 (t, *J* = 6.9 Hz, 1H), 3.76 (s, 6H), 3.09 (td, *J* = 7.0, 1.4 Hz, 2H), 2.36 (s, 3H), 1.90 – 1.43 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.65, 150.23, 143.25, 136.58, 129.16, 126.12, 91.43, 89.46, 55.76, 55.07, 43.84, 36.97, 26.48, 21.00.
HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C19H27N2O2 = 315.2104; found mass = 315.2083.



36

N^4,1,1-triphenylbutane-1,4-diamine

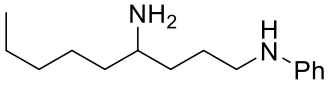
The diamine was synthesized according to General Procedure C using homoallylic amine (mg, mmol, equiv.) and aryl amine (228 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a >20:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (119.1 mg, 0.376 mmol, 75% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.63 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.1 Hz, 4H), 7.31 (t, *J* = 7.7 Hz, 4H), 7.23 (t, *J* = 7.2 Hz, 2H), 7.17 (dd, *J* = 8.6, 7.2 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 2H), 3.11 (t, *J* = 7.1 Hz, 2H), 2.39 – 2.30 (m, 2H), 1.91 (br s, 3H), 1.63 – 1.51 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.68, 148.38, 129.24, 128.19, 126.56, 126.42, 117.20, 112.70, 60.96, 44.36, 39.98, 24.49.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C22H25N2 = 317.2012; found mass = 317.2010.



37

N^1-phenylnonane-1,4-diamine

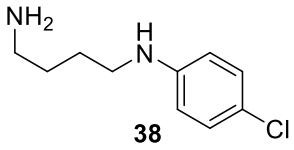
The diamine was synthesized according to General Procedure C using homoallylic amine (70.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (228 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 7.5:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (74.7 mg, 0.319 mmol, 64% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.16 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 7.4 Hz, 2H), 3.12 (t, *J* = 7.0 Hz, 2H), 2.80 – 2.65 (m, 1H), 1.81 – 1.16 (m, 15H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.38, 129.17, 117.08, 112.64, 51.05, 44.10, 38.15, 35.47, 31.95, 26.18, 25.77, 22.62, 14.03.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C15H27N2 = 235.2174; found mass = 235.2184.



38

*N*1-(4-chlorophenyl)butane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (45.8 μL, 0.5 mmol, 1 equiv.) and aryl amine (319 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 3.9:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (63.1 mg, 0.319 mmol, 64% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

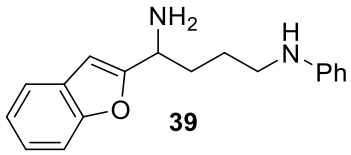
R_f = 0.26 (20:80 MeOH:DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 8.8 Hz, 2H), 3.10 (t, *J* = 7.0 Hz, 2H), 2.75 (t, *J* = 6.9 Hz, 2H), 1.65 (dt, *J* = 13.8, 7.0 Hz, 2H), 1.60 – 1.51 (m, 2H).

Anti-Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.97, 129.01, 121.57, 113.70, 43.91, 41.85, 31.06, 26.77.

Markovnikov Product: ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.21, 129.07, 121.34, 114.20, 47.13, 40.38, 39.18, 20.81.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C10H16N2Cl = 199.1002; found mass = 199.0997.



39

1-(benzofuran-2-yl)-*N*^{4}-phenylbutane-1,4-diamine

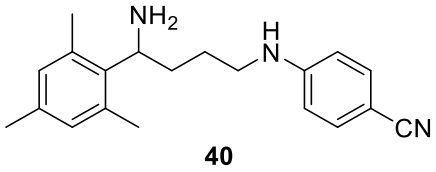
The diamine was synthesized according to General Procedure C using homoallylic amine (93.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (228 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a >20:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (79.0 mg, 0.282 mmol, 56% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.51 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 7.4, 1.5, 0.7 Hz, 1H), 7.44 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.20 (td, *J* = 7.4, 1.2 Hz, 1H), 7.16 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 7.5 Hz, 2H), 6.51 (s, 1H), 4.08 (td, *J* = 6.9, 0.8 Hz, 1H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.02 (dddd, *J* = 13.4, 10.0, 6.7, 5.8 Hz, 1H), 1.89 (dddd, *J* = 13.5, 10.1, 7.0, 5.4 Hz, 1H), 1.82 – 1.46 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.71, 154.65, 148.27, 129.22, 128.33, 123.75, 122.66, 120.73, 117.21, 112.68, 111.04, 101.42, 50.07, 43.77, 33.73, 26.14.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H21N2O = 281.1654; found mass = 281.1663.



40

4-((4-amino-4-mesitylbutyl)amino)benzonitrile

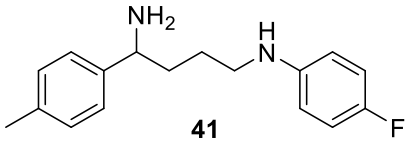
The diamine was synthesized according to General Procedure C using homoallylic amine (94.7 mg, 0.5 mmol, 1 equiv.) and aryl amine (295 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 3.8:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (105.9 mg, 0.344 mmol, 69% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.43 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H), 6.82 (s, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 4.45 (s, 1H), 4.38 (t, *J* = 7.5 Hz, 1H), 3.17 – 3.08 (m, 2H), 2.39 (s, 6H), 2.24 (s, 3H), 1.99 – 1.82 (m, 2H), 1.81 – 1.68 (m, 1H), 1.55 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.36, 138.20, 136.11, 135.70, 133.70, 120.56, 111.99, 98.37, 51.75, 43.29, 33.91, 27.01, 21.23, 20.67.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C20H26N3 = 308.2127; found mass = 308.2129.



41

N^1-(4-fluorophenyl)-4-(*p*-tolyl)butane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (237 μL, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 11.9:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (84.3 mg, 0.310 mmol, 62% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

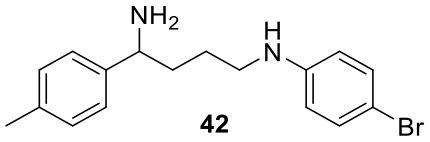
R_f = 0.28 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.86 (t, *J* = 8.8 Hz, 2H), 6.48 (dd, *J* = 9.0, 4.4 Hz, 2H), 3.88 (t, *J* = 6.9 Hz, 1H), 3.05 (td, *J* = 7.2, 1.8 Hz, 2H), 2.34 (s, 3H), 1.88 – 1.35 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.68 (d, *J* = 234.4 Hz), 144.73 (d, *J* = 2.2 Hz), 143.34, 136.68, 129.23, 126.17, 115.59 (d, *J* = 22.5 Hz), 113.42 (d, *J* = 7.5 Hz), 55.85, 44.62, 37.03, 26.58, 21.06.

^{19}F NMR (471 MHz, $CDCl_3$) δ -128.49 (tt, *J* = 8.6, 4.3 Hz).

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H22N2F = 273.1767; found mass = 273.1765.



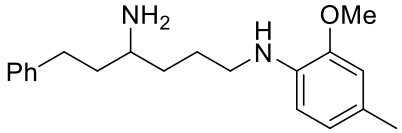
42

N^1-(4-bromophenyl)-4-(*p*-tolyl)butane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (430 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 6.8:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (129.4 mg, 0.388 mmol, 78% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.25 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (m, 4H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.42 (d, *J* = 8.8 Hz, 2H), 3.87 (t, *J* = 6.9 Hz, 1H), 3.05 (td, *J* = 7.3, 1.8 Hz, 2H), 2.34 (s, 3H), 1.86 – 1.40 (m, 7H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 147.27, 143.26, 136.68, 131.83, 129.21, 126.12, 114.14, 108.55, 55.79, 43.88, 36.94, 26.37, 21.04.
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H22N2Br = 333.0966; found mass = 333.0969.



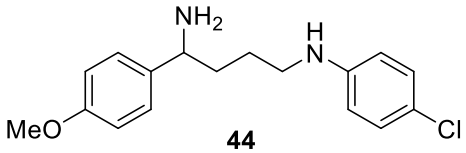
43

N^1-(2-methoxy-4-methylphenyl)-6-phenylhexane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (87.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (343 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 4.1:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (105.6 mg, 0.338 mmol, 68% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.30 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 7.3 Hz, 3H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.51 – 6.41 (m, 2H), 3.81 (s, 3H), 3.13 (t, *J* = 7.0 Hz, 1H), 2.83 – 2.72 (m, 2H), 2.64 (ddd, *J* = 13.7, 10.2, 6.1 Hz, 1H), 2.27 (s, 3H), 1.83 – 1.55 (m, 6H), 1.43 (dddd, *J* = 13.3, 10.5, 7.7, 5.2 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.80, 142.29, 138.13, 130.65, 128.41, 128.36, 125.80, 116.29, 110.86, 109.38, 55.59, 50.75, 43.85, 39.94, 35.69, 32.61, 26.21, 21.20.
HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C20H29N2O = 313.2280; found mass = 313.2290.



44

N^1-(4-chlorophenyl)-4-(4-methoxyphenyl)butane-1,4-diamine

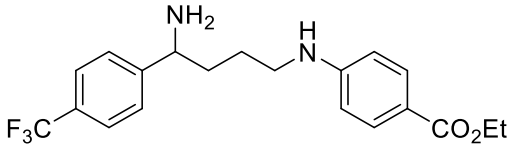
The diamine was synthesized according to General Procedure C using homoallylic amine (88.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (319 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 9.3:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (105.0 mg, 0.344 mmol, 69% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

R_f = 0.22 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 3.87 (t, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 3.05 (td, *J* = 7.3, 2.0 Hz, 2H), 1.93 – 1.36 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.64, 146.86, 138.33, 128.98, 127.27, 121.59, 113.89, 113.65, 55.48, 55.28, 43.99, 37.04, 26.42.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H22N2OCl = 305.1421; found mass = 305.1407.



45

Ethyl 4-((4-amino-4-(4-(trifluoromethyl)phenyl)butyl)amino)benzoate

The diamine was synthesized according to General Procedure C using homoallylic amine (107.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (413 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 3.6:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (159.2 mg, 0.418 mmol, 84% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

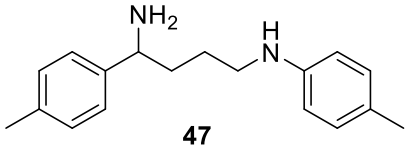
R_f = 0.52 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 9.0 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.18 (s, 1H), 4.00 (t, *J* = 6.7 Hz, 1H), 3.16 (td, *J* = 6.7, 3.2 Hz, 2H), 1.91 – 1.47 (m, 6H), 1.35 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.84, 151.81, 150.17, 131.50, 129.41 (q, *J* = 32.4 Hz), 126.67, 125.53 (q, *J* = 3.8 Hz), 124.16 (q, *J* = 271.2 Hz), 118.60, 111.29, 60.18, 55.75, 43.24, 36.91, 26.11, 14.46.

^{19}F NMR (471 MHz, $CDCl_3$) δ -61.87.

HR-MS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C20H24N2O2F3 = 381.1790; found mass = 381.1788.



47

N^1,4-di-*p*-tolylbutane-1,4-diamine

The diamine was synthesized according to General Procedure C using homoallylic amine (80.6 mg, 0.5 mmol, 1 equiv.) and aryl amine (268 mg, 2.5 mmol, 5 equiv). Analysis of the crude mixture gave the anti-Markovnikov to Markovnikov product as a 11.1:1 mixture. The product was isolated after column chromatography as outlined in General Procedure C (74.7 mg, 0.278 mmol, 56% yield). ^{1}H NMR collected in C_6D_6 confirmed the removal of chloroform.

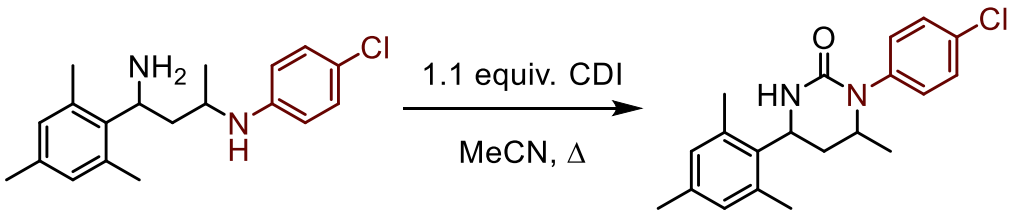
Rf= 0.49 (10:90 MeOH:CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 2H), 3.90 (t, *J* = 6.9 Hz, 1H), 3.09 (ddd, *J* = 8.5, 6.7, 2.0 Hz, 2H), 2.36 (s, 3H), 2.25 (s, 3H), 1.87 – 1.46 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.13, 143.40, 136.62, 129.69, 129.20, 126.35, 126.20, 112.88, 55.86, 44.31, 37.10, 26.68, 21.06, 20.37.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2 = 269.2018; found mass = 269.2007.

Assigning the Major Diastereomer for Markovnikov-Selective Conditions

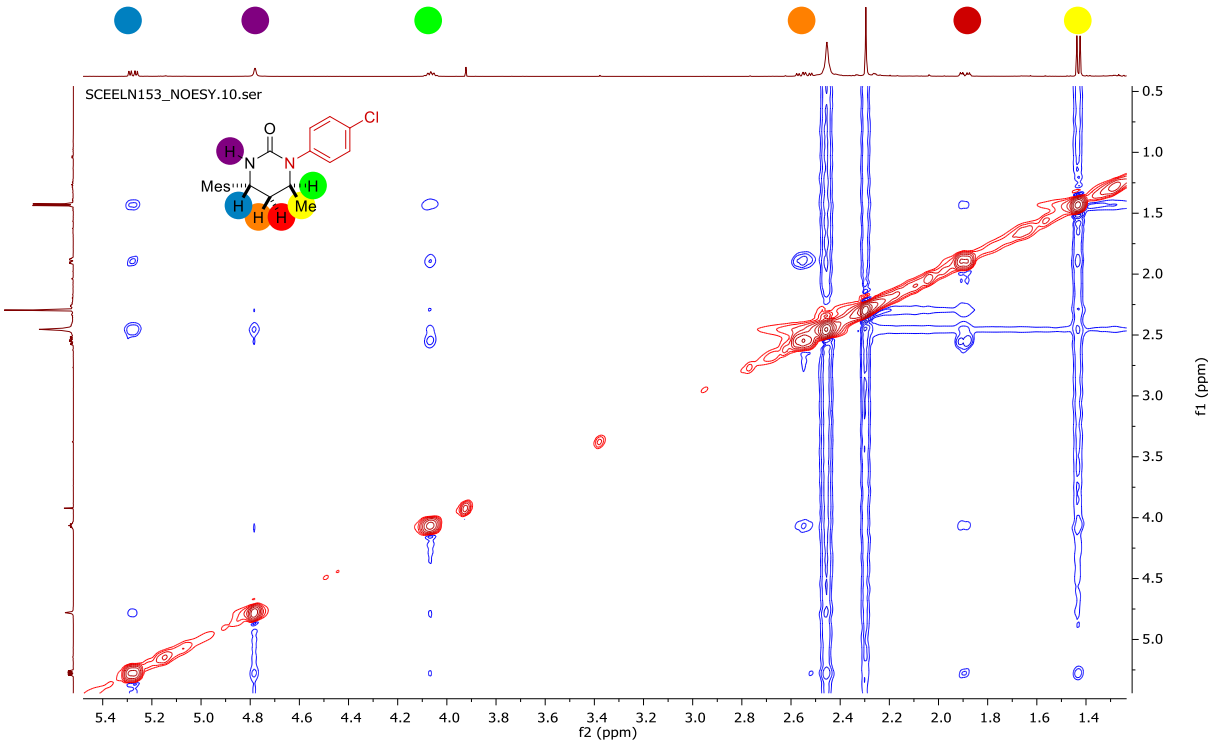


To a 20 mL vial equipped with stir bar was added acetonitrile (1.63 mL, 0.2 M), diamine (103.3 mg, 0.325 mmol, 1 equiv), and CDI (58.0 mg, 0.357 mmol, 1.1 equiv). The 20 mL vial was sealed with a teflon cap and heated to 60 °C overnight. The crude reaction mixture was cooled to room temperature, solvent was removed *en vacuo*, and column chromatography (125 mL silica 0:100 → 4:96 MeOH:$CHCl_3$) gave the purified product as a light yellow solid (91.8 mg, 0.268 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.8 Hz, 2H), 7.28 – 7.26 (m, 2H), 6.87 (s, 2H), 5.25 (dd, *J* = 12.3, 4.9 Hz, 1H), 4.76 (s, 1H), 4.04 (qdd, *J* = 6.6, 4.8, 2.1 Hz, 1H), 2.52 (ddd, *J* = 13.5, 12.3, 5.0 Hz, 1H), 2.43 (s, 6H), 2.27 (s, 3H), 1.87 (ddt, *J* = 13.5, 4.9, 1.9 Hz, 1H), 1.41 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.72, 141.26, 137.52, 136.38, 133.06, 131.61, 130.47, 129.19, 128.57, 54.21, 48.08, 32.36, 20.87, 20.67, 19.30.

The purified compound was dissolved in d_1-$CDCl_3$ and analyzed by 2D-NOESY.



To provide unambiguous assignment of the major diastereomer, the product was crystallized by slow evaporation from $CDCl_3$and the structure was assigned by single crystal X-Ray diffraction.

ORTEP representation. Hydrogen atoms omitted for clarity. A second unique molecule was found in the unit cell and is omitted for clarity. Thermal ellipsoids are drawn at 50% probability level.

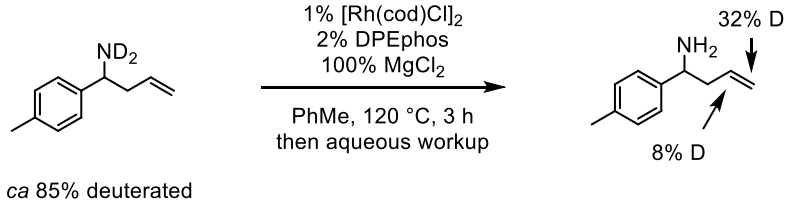
Crystallographic data

Empirical formula	$C_{20}H_{23}ClN_2O$	
Formula weight	342.85	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P $2_1/n$	
Unit cell dimensions	a = 12.2380(5)	b = 16.5194(6)
c = 17.9179(7)	α = 90°, β = 96.4861(15)°, γ = 90°	
Volume	3599.2(2)	
Z	8	
Density (calculated)	1.265 g/cm^3	
Absorption coefficient	0.221 mm^{-1}	
F(000)	1456.0	
Crystal size	0.316 x 0.294 x 0.26 mm^3	

Theta range for data collection	2.132 to 25.702°
Index ranges	-14<=h<=14, -20<=k<=20, -21<=l<=21
Reflections collected	6791
Independent reflections	5449 [R(int) = 0.0395]
Completeness to theta	0.995
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/ restraints/ parameters	5449/ 0/ 442
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.0937

Deuterium Incorporation Studies

Demonstrating background deuteration of starting material under Markovnikov selective conditions in the absence of aryl amine:

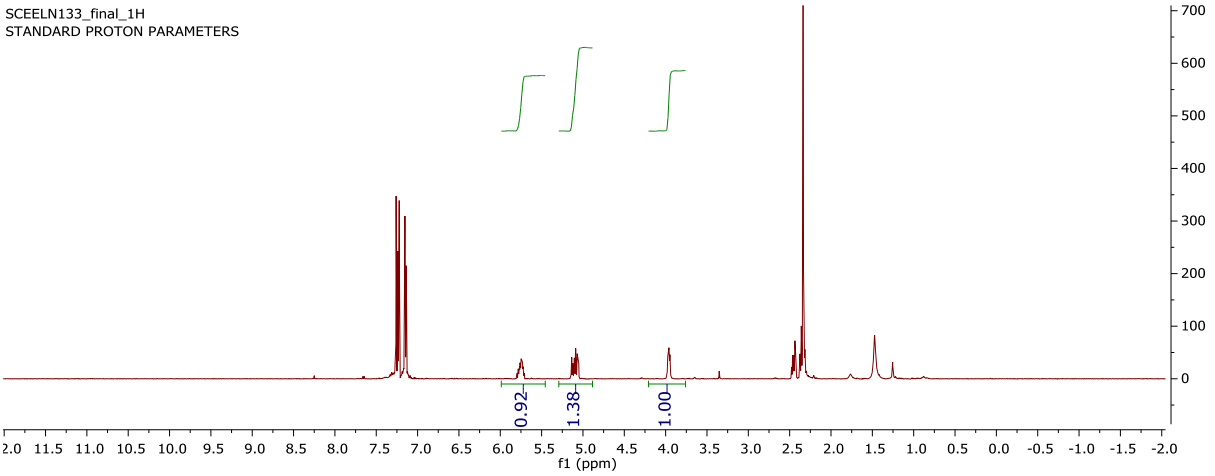


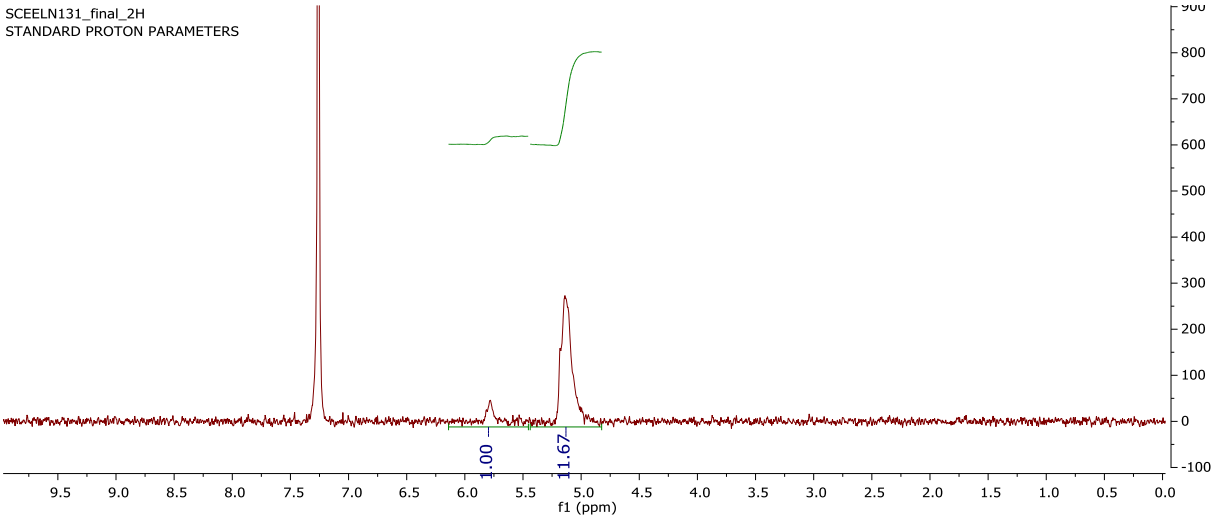
ca 85% deuterated

To a 4 mL vial equipped with stir bar was added [Rh(cod)Cl]2 (2.47 mg, 5.00 μmol, 1 mol %), DPEphos (5.39 mg, 10.0 μmol, 2 mol %), homoallylic amine (81.6 mg, 0.500 mmol, 1 equiv.), and PhMe (500 μL). The vial was sealed with a Teflon cap, removed from the glove box, heated to 120 °C for 60 seconds, cooled to room temperature, returned to the glove box, uncapped, and MgCl2 (47.6 mg, 0.500 mmol, 1 equiv.) was then added. The vial was resealed with a Teflon cap, removed from the glove box, and heated to 120 °C for 3 h.

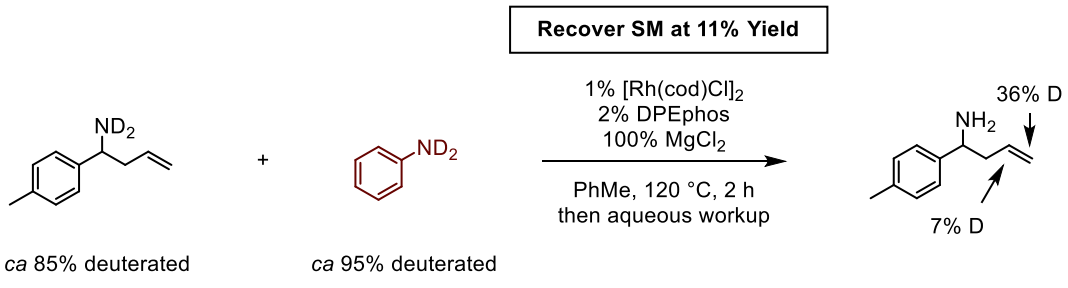
The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The mixture was then diluted with 50 mL each half-saturated K_2CO_3 (aq) and $CHCl_3$, and the aqueous layer was extracted 3 x 50 mL $CHCl_3$. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. A yellow oil was obtained.

^{1}H NMR demonstrates that the product is 8% deuterated at the internal position of the alkene and 32% deuterated at the terminal position of the alkene. ^{2}H NMR shows that deuteration is not observed at any other position of the substrate.





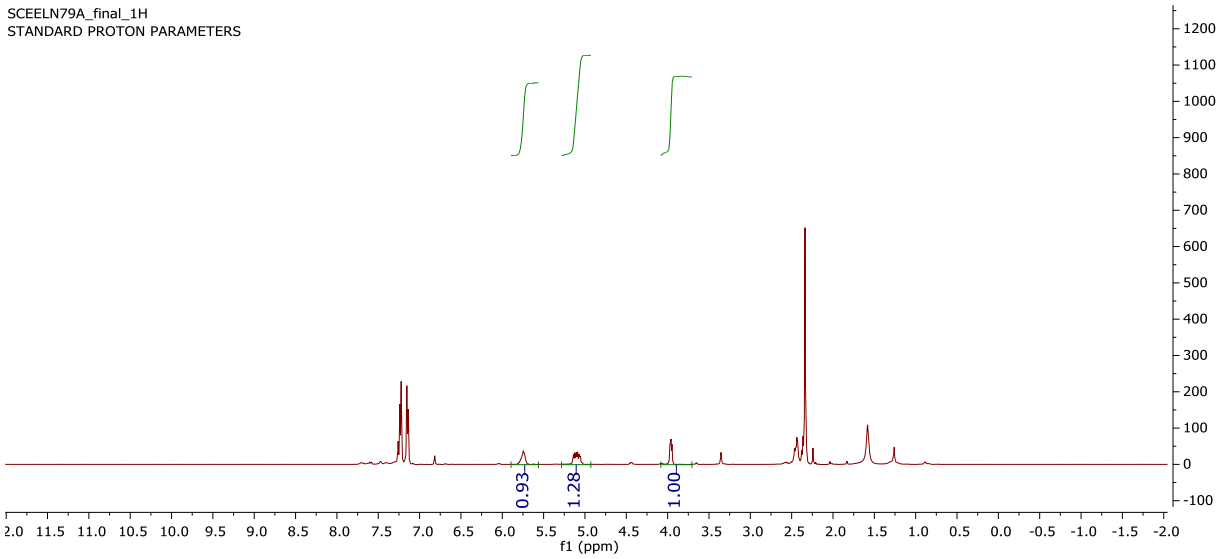
Demonstrating background deuteration of starting material under Markovnikov selective conditions in the presence of aryl amine:

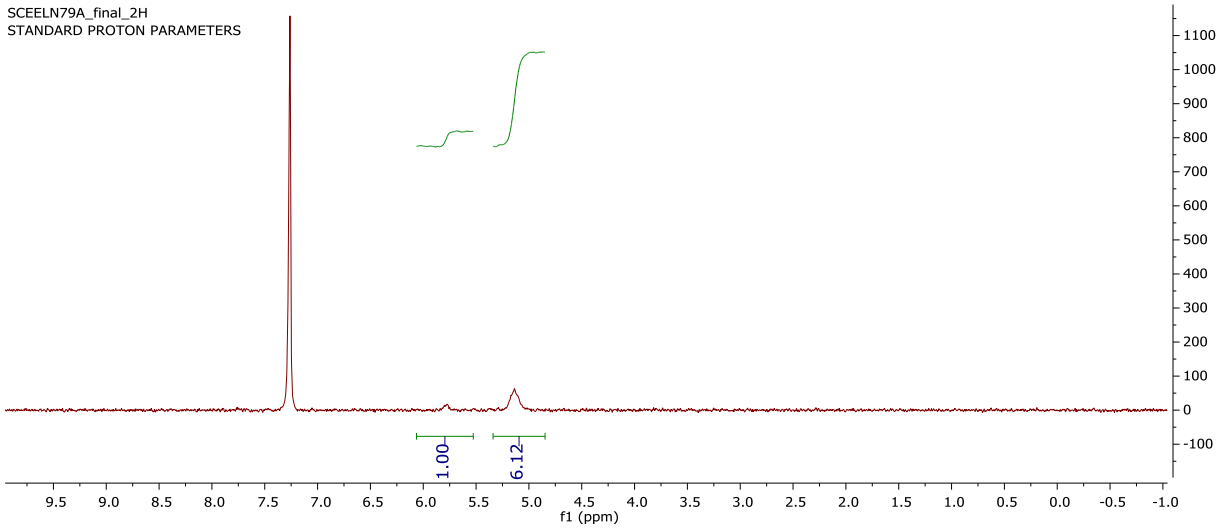


To a 4 mL vial equipped with stir bar was added [Rh(cod)Cl]2 (2.47 mg, 5.00 μmol, 1 mol %), DPEphos (5.39 mg, 10.0 μmol, 2 mol %), homoallylic amine (81.6 mg, 0.500 mmol, 1 equiv.), deuterated aniline (238 mg, 2.50 mmol, 5 equiv.), and PhMe (500 μL). The vial was sealed with a Teflon cap, removed from the glove box, heated to 120 °C for 60 seconds, cooled to room temperature, returned to the glove box, uncapped, and MgCl2 (47.6 mg, 0.500 mmol, 1 equiv.) was then added. The vial was resealed with a Teflon cap, removed from the glove box, and heated to 120 °C for 2 h.

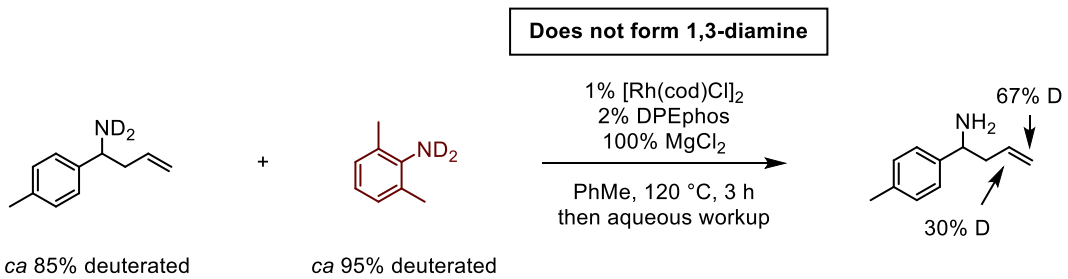
The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The mixture was then diluted with 50 mL each half-saturated K_2CO_3 (aq) and $CHCl_3$, and the aqueous layer was extracted 3 x 50 mL $CHCl_3$. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (100 mL silica in a 4.5 cm diameter column with 2% sat. NH_4OH : 98% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 2% sat. NH_4OH : 98% $CHCl_3$ to 2% sat. NH_4OH : 5% MeOH : 93% $CHCl_3$ as the eleutant) gave the desired product as a yellow oil.

^1H NMR demonstrates that the product is 7% deuterated at the internal position of the alkene and 36% deuterated at the terminal position of the alkene. ^2H NMR shows that deuteration is not observed at any other position of the substrate.





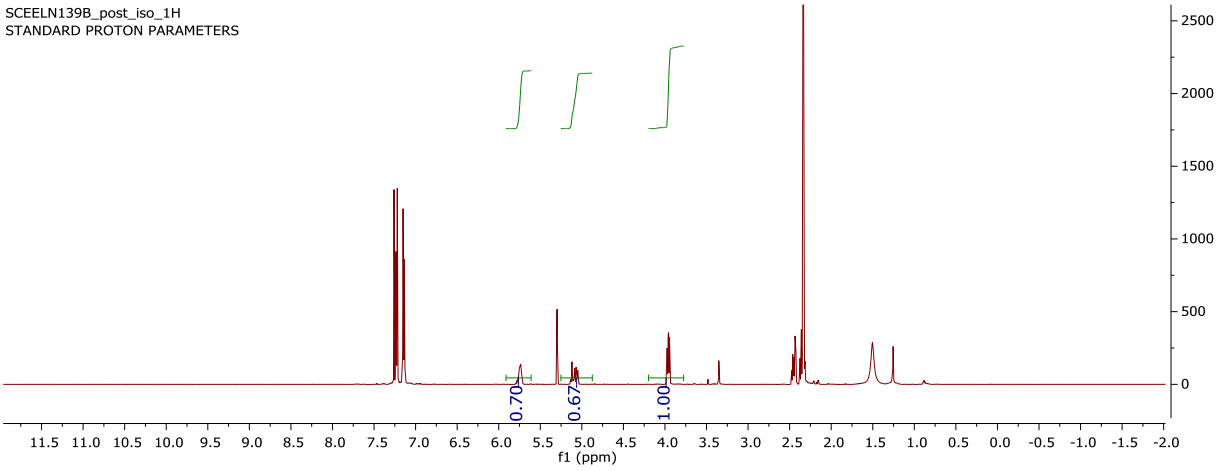
Demonstrating background deuteration of starting material under Markovnikov selective conditions in the presence of aryl amine that does not undergo the hydroamination reaction:

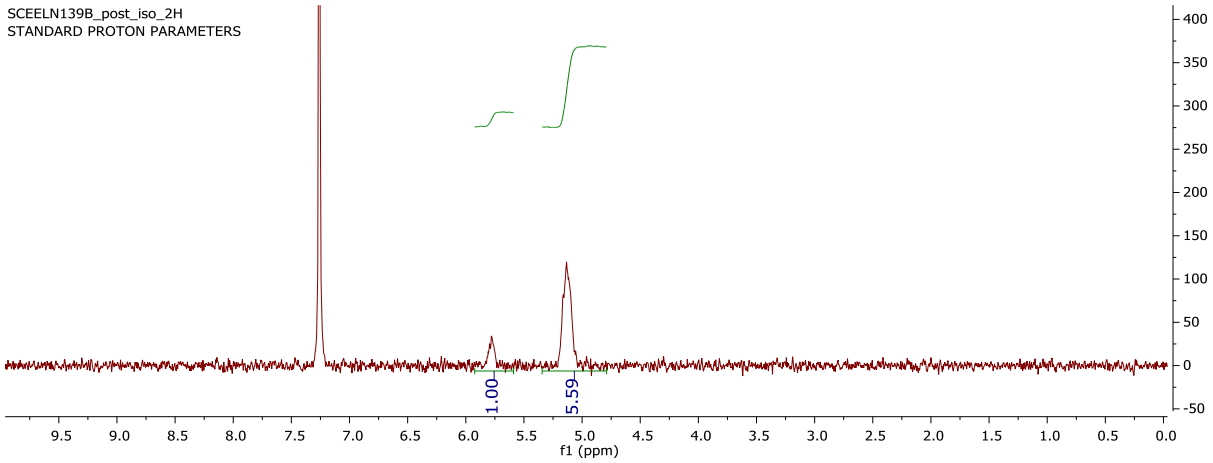


To a 4 mL vial equipped with stir bar was added [Rh(cod)Cl]2 (2.47 mg, 5.00 µmol, 1 mol %), DPEphos (5.39 mg, 10.0 µmol, 2 mol %), homoallylic amine (81.6 mg, 0.500 mmol, 1 equiv.), deuterated aniline (308 mg, 2.50 mmol, 5 equiv.), and PhMe (500 µL). The vial was sealed with a Teflon cap, removed from the glove box, heated to 120 °C for 60 seconds, cooled to room temperature, returned to the glove box, uncapped, and MgCl2 (47.6 mg, 0.500 mmol, 1 equiv.) was then added. The vial was resealed with a Teflon cap, removed from the glove box, and heated to 120 °C for 3 h.

The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The mixture was then diluted with 50 mL each half-saturated K_2CO_3 (aq) and $CHCl_3$, and the aqueous layer was extracted 3 x 50 mL $CHCl_3$. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (100 mL silica in a 4.5 cm diameter column with 2% sat. NH_4OH : 98% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 2% sat. NH_4OH : 98% $CHCl_3$ to 2% sat. NH_4OH : 5% MeOH : 93% $CHCl_3$ as the eleutant) gave the desired product as a yellow oil.

^{1}H NMR demonstrates that the product is 30% deuterated at the internal position of the alkene and 67% deuterated at the terminal position of the alkene. ^{2}H NMR shows that deuteration is not observed at any other position of the substrate.




SCEELN139B_post_iso_2H
STANDARD PROTON PARAMETERS
400
350
300
250
200
150
100
50
0
-50
1.00
5.59
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
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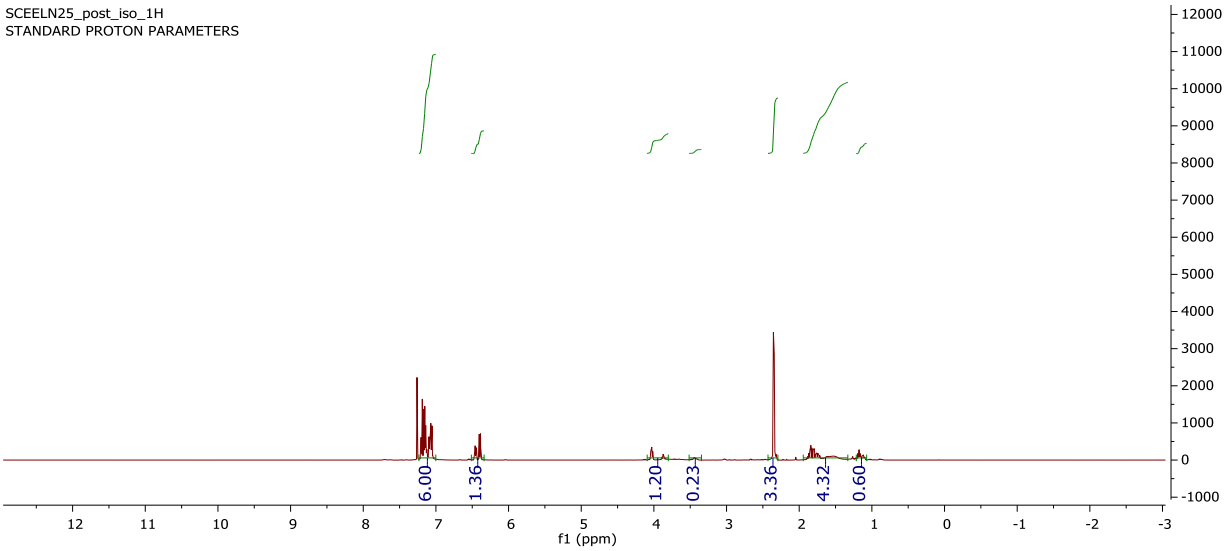
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

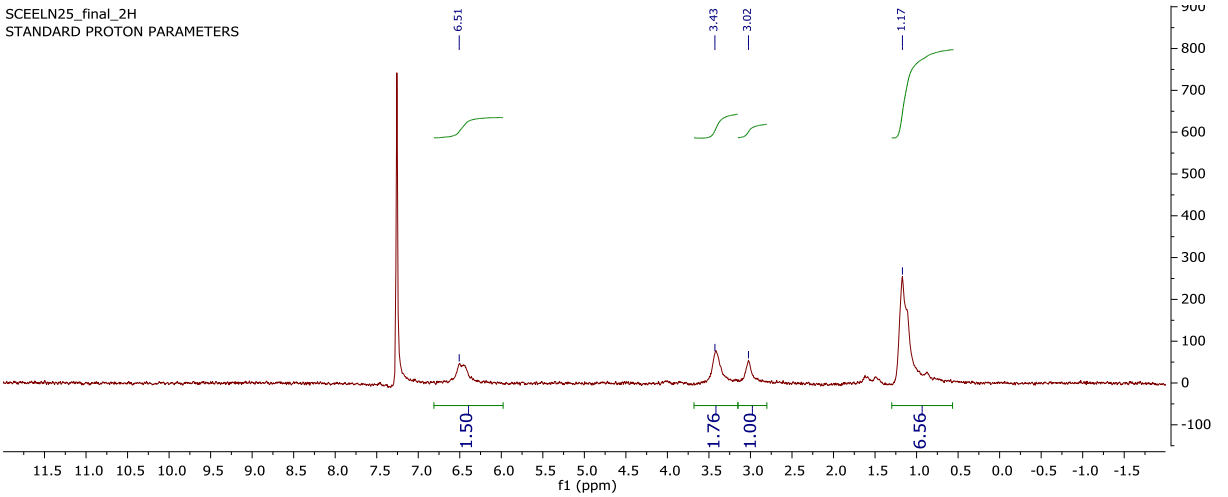
Isolating product under Markovnikov selective conditions demonstrates excess deuterium incorporation into the product.

To a 4 mL vial equipped with stir bar was added [Rh(cod)Cl]2 (9.86 mg, 20.0 μmol, 4 mol %), DPEphos (21.6 mg, 40.0 μmol, 8 mol %), homoallylic amine (81.6 mg, 0.500 mmol, 1 equiv.), deuterated aniline (324 mg, 2.50 mmol, 5 equiv.), and PhMe (500 μL). The vial was sealed with a Teflon cap, removed from the glove box, heated to 120 °C for 60 seconds, cooled to room temperature, returned to the glove box, uncapped, and MgCl2 (47.6 mg, 0.500 mmol, 1 equiv.) was then added. The vial was resealed with a Teflon cap, removed from the glove box, and heated to 120 °C for 3 h.

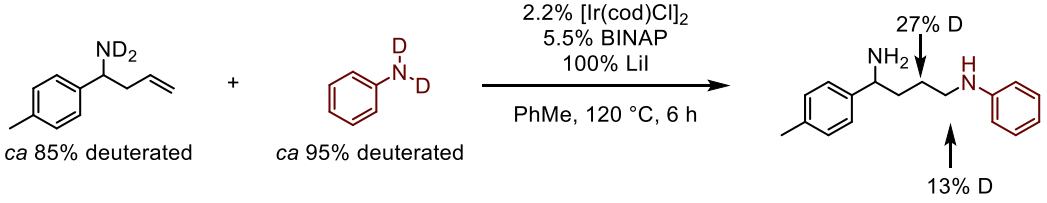
The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The mixture was then diluted with 50 mL each half-saturated K_2CO_3 (aq) and $CHCl_3$, and the aqueous layer was extracted 3 x 50 mL $CHCl_3$. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (100 mL silica in a 4.5 cm diameter column with 2% sat. NH_4OH : 98% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 2% sat. NH_4OH : 98% $CHCl_3$ to 2% sat. NH_4OH : 5% MeOH : 93% $CHCl_3$ as the eleutant) gave the desired product as a yellow oil (63.5 mg, 0.218 mmol) in 44% yield.

^{1}H NMR demonstrates that the product is 77% deuterated ipso to the aniline nucleophile (the two signals observed likely correspond to the two diastereomers,) 80% deuterated at what was the terminal position of the alkene, and 32% deuterated at the *ortho* position. ^{2}H NMR shows that deuteration is not observed at any other position of the substrate.





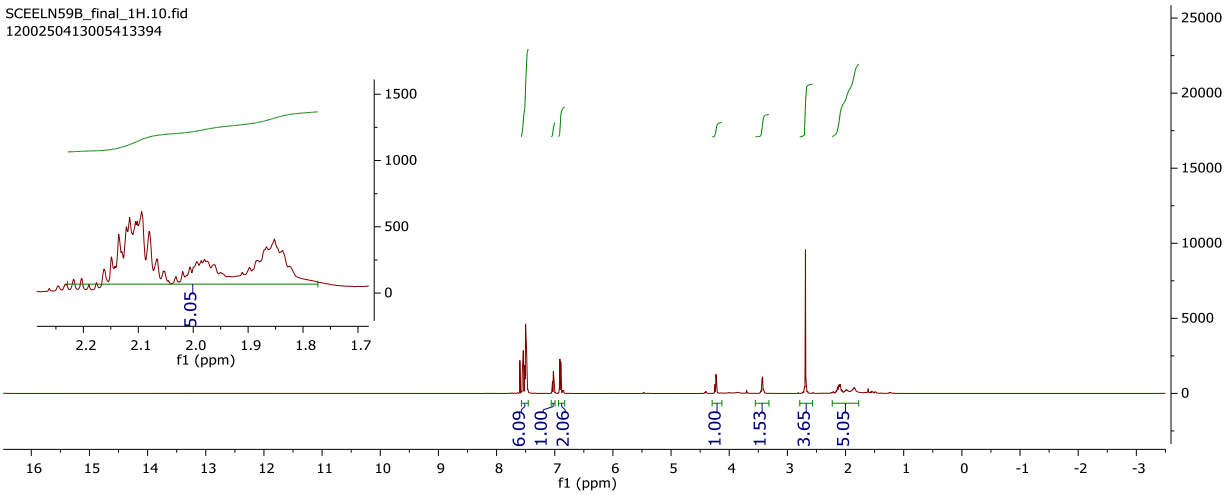
Isolating product under anti-Markovnikov selective conditions demonstrates incorporation of less than one deuterium into the product.

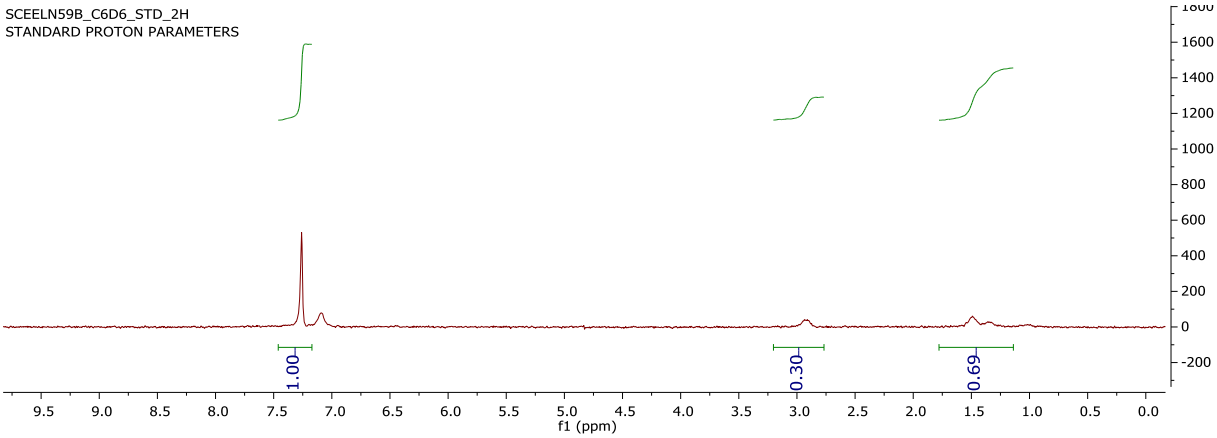


To a 4 mL vial equipped with stir bar was added $[Ir(cod)Cl]_2$ (7.39 mg, 11.0 μmol, 2.2 mol %), (±)-BINAP (17.1 mg, 27.5 μmol, 5.5 mol %), lithium iodide (66.9 mg, 0.5 mmol, 1 equiv), toluene (250. μL), homoallylic amine (81.6 mg, 0.5 mmol, 1 equiv.) and deuterated aniline (238 mg, 2.5 mmol, 5 equiv.). The 4 mL vial was sealed with Teflon cap, removed from nitrogen filled glove box, and heated to 120 °C for 6 h while stirring.

The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 15 minutes. The mixture was then diluted with 50 mL each half-saturated K_2CO_3 (aq) and $CHCl_3$, and the aqueous layer was extracted 3 x 50 mL $CHCl_3$. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (100 mL silica in a 4.5 cm diameter column with 2% sat. NH_4OH : 98% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 2% sat. NH_4OH : 98% $CHCl_3$ to 2% sat. NH_4OH : 5% MeOH : 93% $CHCl_3$ as the eleutant) gave a mixture of Markovnikov and anti-Markovnikov products. The product was isolated as a yellow oil (87.1 mg, 0.338 mmol) in 68% yield.

Due to overlapping signals in the proton NMR, the extent of deuteration of the product could not be determined. However, ^2H NMR was collected with 15 μL of CDCl3 as an internal standard in H_6-Benzene. Integration of these peaks relative to the internal standard demonstrates that the product is 13% deuterated ipso to the aniline nucleophile and 27% deuterated adjacent to the aniline nucleophile. Deuteration at other sites of the product is not observed.





Initial Rate Kinetic Isotope Effect Studies

Markovnikov Hydroamination Procedure for ^{1}H-substrates

A stock solution was prepared with $[Rh(cod)Cl]_2$ (0.01X), DPEphos (0.02X), toluene (1 M), homoallylic amine (X), and aniline (5X). To individual 4 mL vials equipped with stir bars was added $MgCl_2$ (9.52 mg, 0.1 mmol, 1 equiv.) and aliquot from stock solution (165 µL). The vials were sealed with a teflon cap, removed from the glove box, and heated to 120 °C for the specified time. The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, diphenylmethane (5 µL, 30.0 µmol) was added as an internal standard, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The crude organic layer was analyzed (triplicate runs injected three times each).

Markovnikov Hydroamination Procedure for ^{2}H-substrates

A stock solution was prepared with [Rh(cod)Cl] (0.01X), DPEPhos (0.02X), toluene (1 M), deuterated homoallylic amine (X), and deuterated aniline (5X). To individual 4 mL vials equipped with stir bars was added $MgCl_2$ (9.52 mg, 0.1 mmol, 1 equiv.) and aliquot from stock solution (165 μL). The vials were sealed with a teflon cap, removed from the glove box, and heated to 120 °C for the specified time. The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, diphenylmethane (5 μL, 30.0 μmol) was added as an internal standard, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The crude organic layer was analyzed (triplicate runs injected three times each).

Anti-Markovnikov Hydroamination Procedure for ^{1}H-substrates

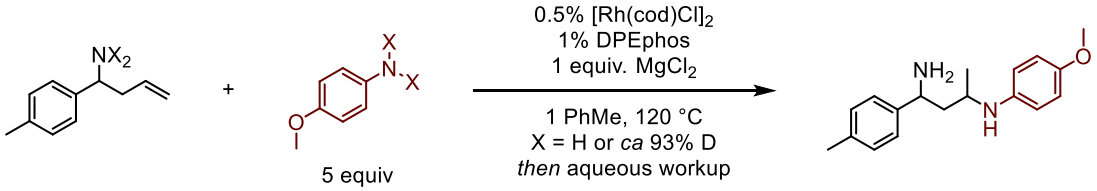
A stock solution was prepared with [Ir(cod)Cl] (0.005X), (±)-BINAP (0.0125X), toluene (1 M), homoallylic amine (X), and aniline (5X). To individual 4 mL vials equipped with stir bars was added lithium iodide (13.4 mg, 0.1 mmol, 1 equiv.) and aliquot from stock solution (165 μL). The vials were sealed with a teflon cap, removed from the glove box, and heated to 120 °C for the specified time. The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, diphenylmethane (5 μL, 30.0 μmol) was added as an internal standard, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 15 minutes. The crude organic layer was analyzed (triplicate runs injected three times each).

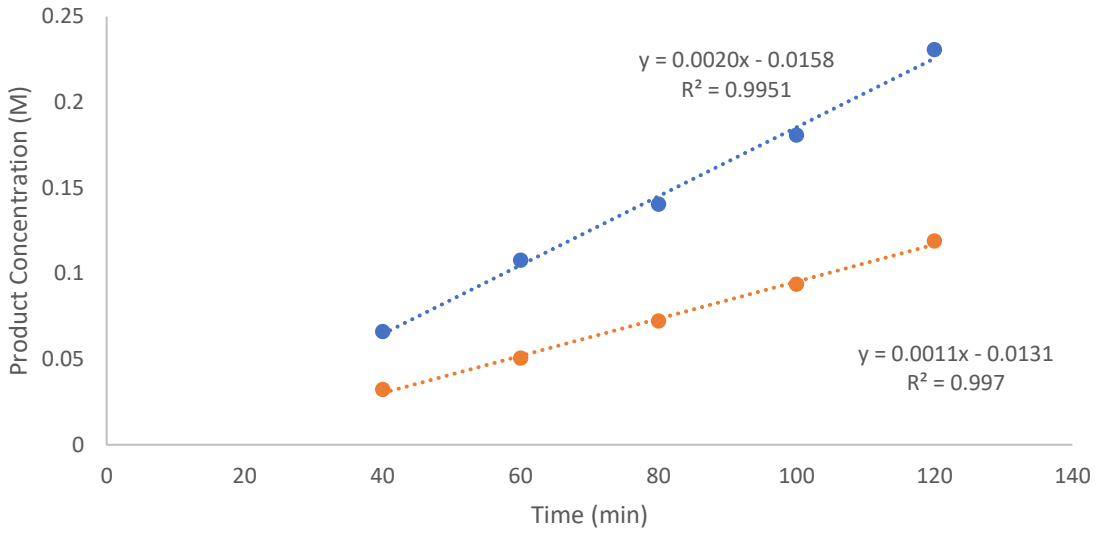
Anti-Markovnikov Hydroamination Procedure for ^{2}H-substrates

A stock solution was prepared with $[Ir(cod)Cl]_2$ (0.005X), (±)-BINAP (0.0125X), toluene (1 M), deuterated homoallylic amine (X), and deuterated aniline (5X). To individual 4 mL vials equipped with stir bars was added lithium iodide (13.4 mg, 0.1 mmol, 1 equiv.) and aliquot from stock solution (165 μL). The vials were sealed with a teflon cap, removed from the glove box, and heated to 120 °C for the specified time. The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, diphenylmethane (5 μL, 30.0 μmol) was added as an internal standard, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the

slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 15 minutes. The crude organic layer was analyzed (triplicate runs injected three times each).

Markovnikov Hydroamination: *para*-methoxyaniline and *para*-tolylhomoallyl amine





Run	H_2 R1	H_2 R2	H_2 R3	D_2 R1	D_2 R2	D_2 R3
Rate	$1.86*10^{-3}$	$2.09*10^{-3}$	$2.06*10^{-3}$	$1.10*10^{-3}$	$1.08*10^{-3}$	$1.06*10^{-3}$
Standard Error	$8.59*10^{-5}$	$1.90*10^{-5}$	$7.98*10^{-5}$	$3.86*10^{-5}$	$3.49*10^{-5}$	$7.67*10^{-5}$

$$k_{(H/D)} = 1.85 \pm 0.06$$

Sample Calculations:

$$k_H \left\{ \frac{1.86 * 10^{-3} + 2.09 * 10^{-3} + 2.06 * 10^{-3}}{3} = 2.00 * 10^{-3} \right.$$

$$k_D \left\{ \frac{1.10 * 10^{-3} + 1.08 * 10^{-3} + 1.06 * 10^{-3}}{3} = 1.08 * 10^{-3} \right.$$

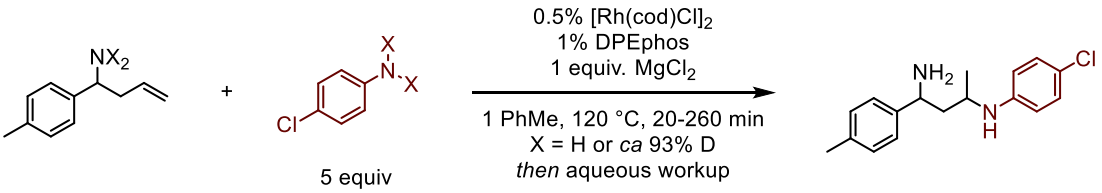
$$\frac{k_H}{k_D} = \frac{2.00}{1.08} = 1.85$$

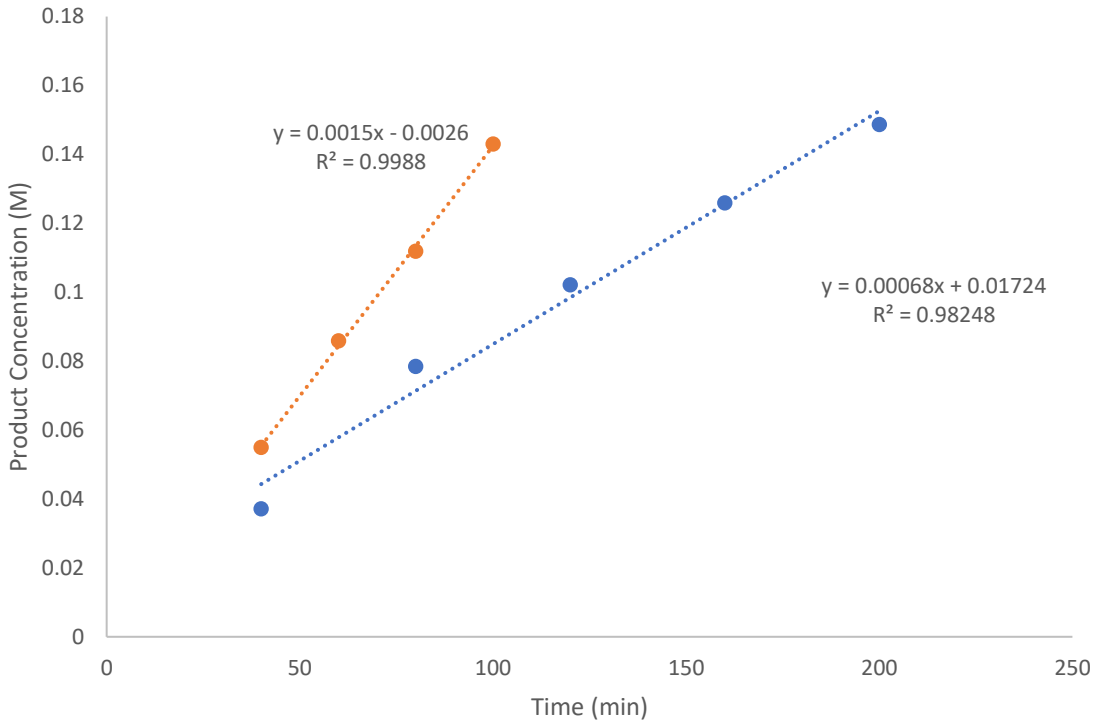
$$s_{k_H} \left\{ \frac{\sqrt{8.59 * 10^{-5} + 1.90 * 10^{-5} + 7.98 * 10^{-5}}}{3} = 3.96 * 10^{-5} \right.$$

$$s_{k_D} \left\{ \frac{\sqrt{3.86 * 10^{-5} + 3.49 * 10^{-5} + 7.67 * 10^{-5}}}{3} = 3.09 * 10^{-5} \right.$$

$$s_{k_{H/D}} = 1.85 \sqrt{\left(\frac{3.96 * 10^{-5}}{0.00200}\right)^2 + \left(\frac{3.09 * 10^{-5}}{0.00108}\right)^2} = 0.06$$

Markovnikov Hydroamination: *para*-chloroaniline and *para*-tolylhomoallyl amine

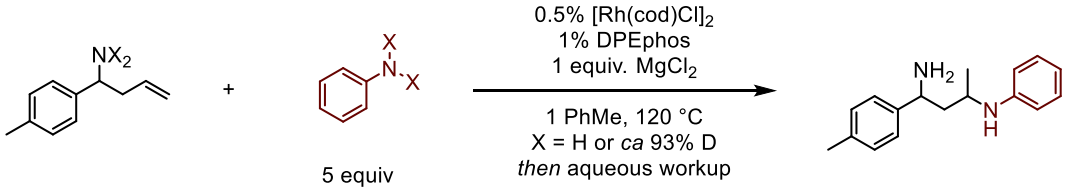


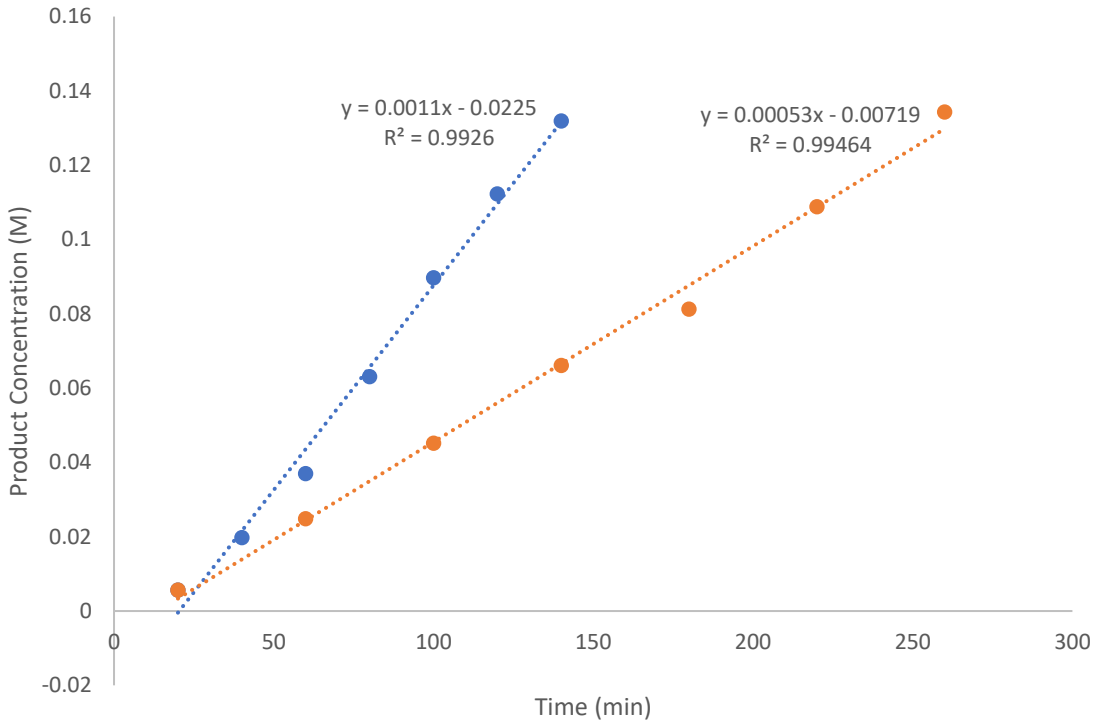


Run	H_2 R1	H_2 R2	H_2 R3	D_2 R1	D_2 R2	D_2 R3
Rate	$1.53*10^{-3}$	$1.18*10^{-3}$	$1.22*10^{-3}$	$0.642*10^{-3}$	$0.629*10^{-3}$	$0.575*10^{-3}$
Standard Error	$7.73*10^{-5}$	$9.00*10^{-5}$	$9.76*10^{-5}$	$7.71*10^{-5}$	$5.78*10^{-5}$	$4.75*10^{-5}$

$$k_{(H/D)} = 2.13 \pm 0.15$$

Markovnikov Hydroamination: Aniline and *para*-tolylhomoallyl amine

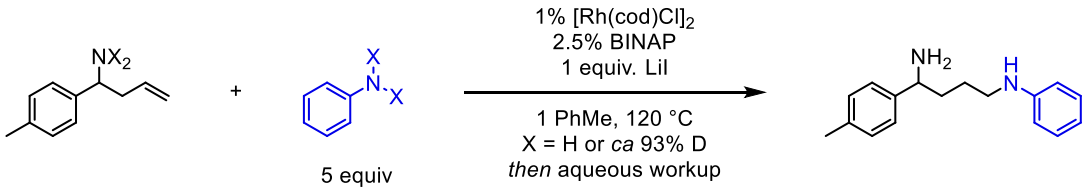


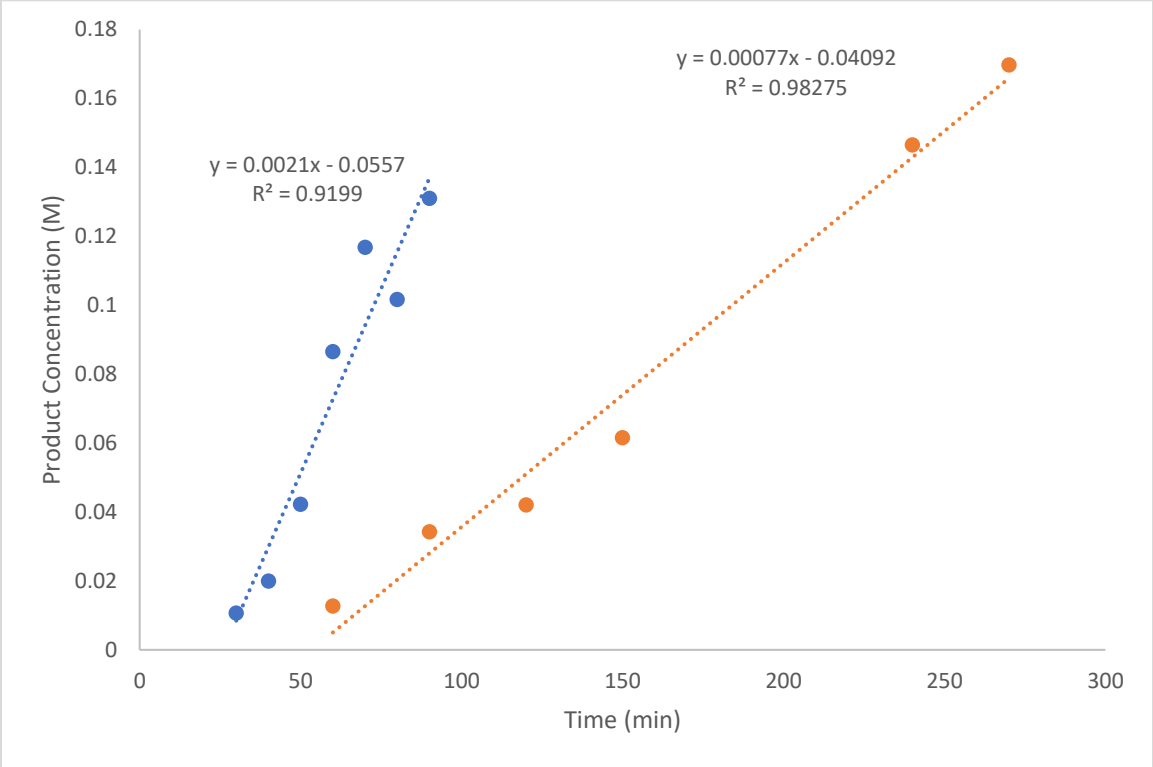


Run	H_2 R1	H_2 R2	H_2 R3	D_2 R1	D_2 R2	D_2 R3
Rate	$0.941*10^{-3}$	$1.10*10^{-3}$	$1.26*10^{-3}$	$0.641*10^{-3}$	$0.594*10^{-3}$	$0.346*10^{-3}$
Standard Error	$6.62*10^{-5}$	$2.14*10^{-5}$	$8.82*10^{-5}$	$5.04*10^{-5}$	$3.43*10^{-5}$	$2.46*10^{-5}$

$$k_{(H/D)} = 2.09 \pm 0.11$$

Anti-Markovnikov Hydroamination: Aniline and *para*-tolylhomoallyl amine





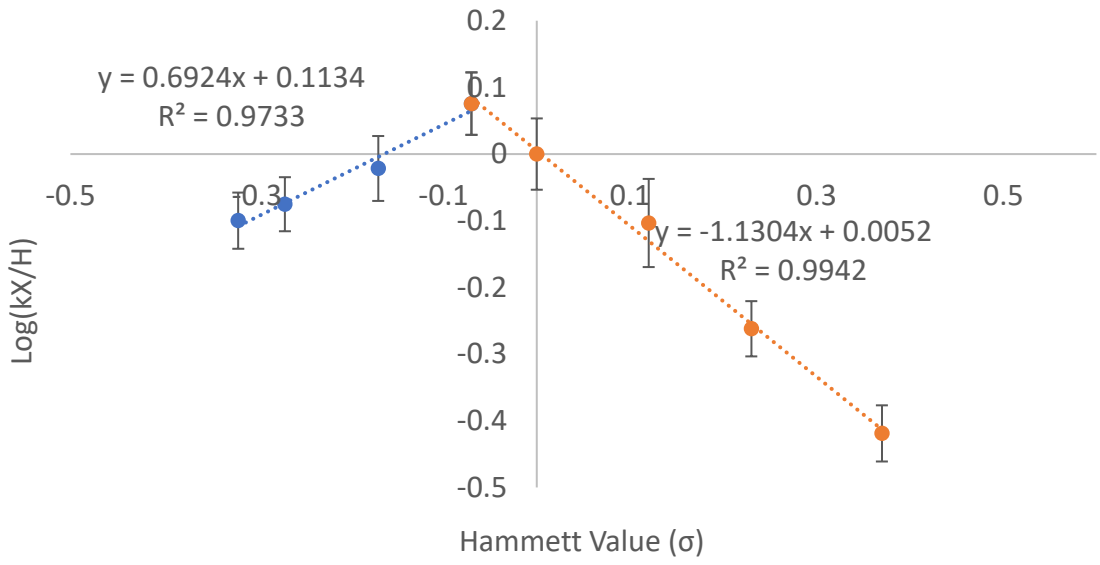
Run	H_2 R1	H_2 R2	H_2 R3	D_2 R1	D_2 R2	D_2 R3
Rate	$2.30*10^{-3}$	$1.66*10^{-3}$	$1.52*10^{-3}$	$0.865*10^{-3}$	$0.637*10^{-3}$	$0.795*10^{-3}$
Standard Error	$2.44*10^{-4}$	$2.86*10^{-4}$	$3.97*10^{-4}$	$0.898*10^{-4}$	$0.780*10^{-4}$	$1.34*10^{-4}$

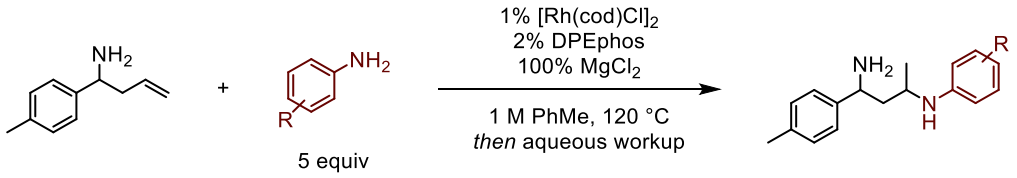
$$k_{(H/D)} = 2.39 \pm 0.30$$

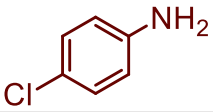
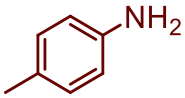
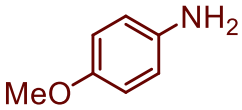
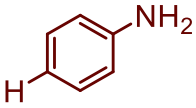
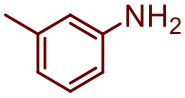
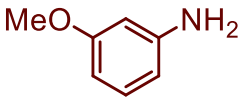
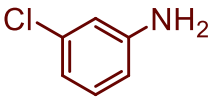
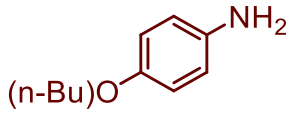
Hammett Studies

Hammett Studies for Markovnikov Selective Conditions

A stock solution was prepared with $[Rh(cod)Cl]_2$ (0.01X), DPEphos (0.02X), toluene (1 M), and **1a** (X). To individual 4 mL vials equipped with stir bars was added $MgCl_2$ (9.52 mg, 0.1 mmol, 1 equiv.), aryl amine (0.5 mmol, 5 equiv.) and aliquot from stock solution (125 µL). The vials were sealed with a teflon cap, removed from the glove box, and heated to 120 °C for the specified time. The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, diphenylmethane (5 µL, 30.0 µmol) was added as an internal standard, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 45 minutes. The crude organic layer was analyzed in duplicate by gas chromatography.

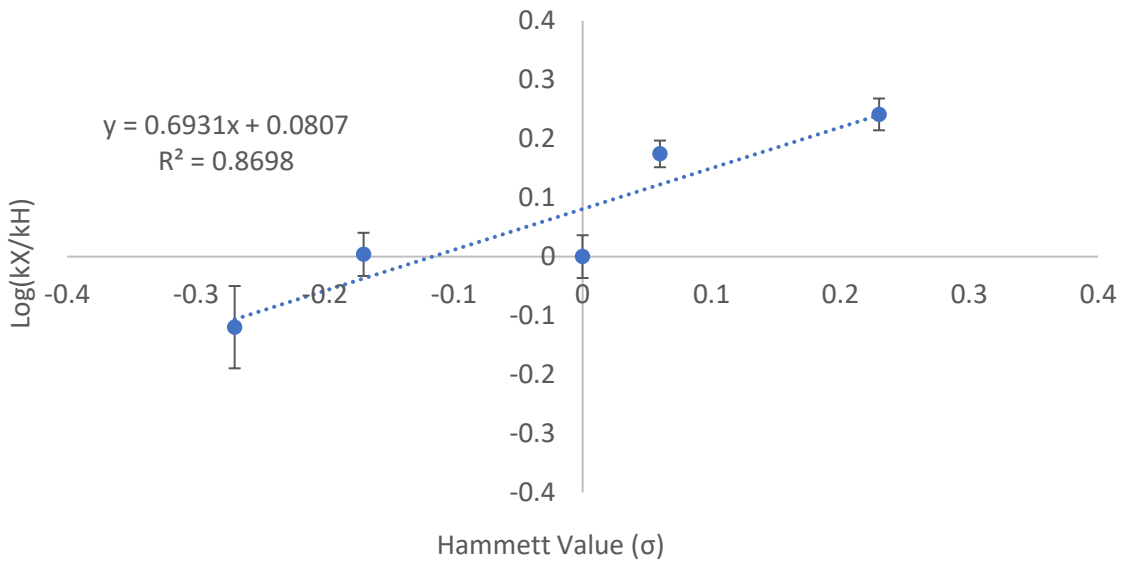


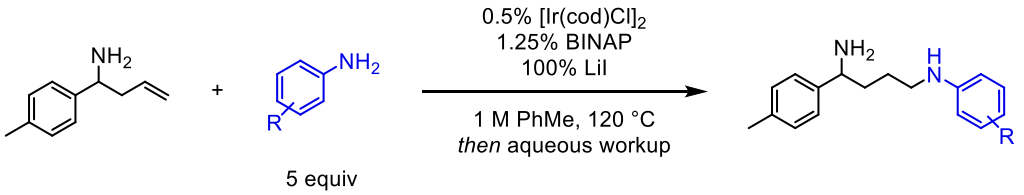


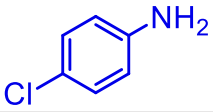
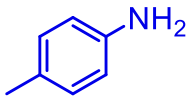
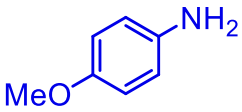
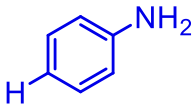
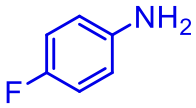
Aniline	Run	Slope	Standard Error
	**1**	$1.45*10^{-3}$	$7.33*10^{-5}$
	2	$1.12*10^{-3}$	$8.54*10^{-5}$
	3	$1.16*10^{-3}$	$9.25*10^{-5}$
	**1**	$2.23*10^{-3}$	$1.66*10^{-4}$
	2	$2.17*10^{-3}$	$4.01*10^{-4}$
	3	$2.09*10^{-3}$	$1.49*10^{-4}$
	**1**	$2.06*10^{-3}$	$1.31*10^{-4}$
	2	$1.83*10^{-3}$	$1.18*10^{-4}$
	3	$1.84*10^{-3}$	$7.88*10^{-5}$
	**1**	$2.24*10^{-3}$	$2.39*10^{-4}$
	2	$2.08*10^{-3}$	$2.99*10^{-4}$
	3	$2.50*10^{-3}$	$4.54*10^{-4}$
	**1**	$2.16*10^{-3}$	$2.47*10^{-4}$
	2	$3.04*10^{-3}$	$3.61*10^{-4}$
	3	$2.91*10^{-3}$	$2.77*10^{-4}$
	**1**	$1.62*10^{-3}$	$4.49*10^{-4}$
	2	$2.08*10^{-3}$	$4.55*10^{-4}$
	3	$1.67*10^{-3}$	$2.08*10^{-4}$
	**1**	$7.68*10^{-4}$	$6.09*10^{-5}$
	2	$9.80*10^{-4}$	$8.20*10^{-5}$
	3	$8.51*10^{-4}$	$4.35*10^{-5}$
	**1**	$1.89*10^{-3}$	$1.41*10^{-4}$
	2	$1.59*10^{-3}$	$1.68*10^{-4}$
	3	$1.95*10^{-3}$	$7.60*10^{-5}$

Hammett Studies for anti-Markovnikov Selective Conditions

A stock solution was prepared with $[Ir(cod)Cl]_2$ (0.005X), (±)-BINAP (0.0125X), toluene (1 M), and homoallylic amine (X). To individual 4 mL vials equipped with stir bars was added lithium iodide (13.4 mg, 0.1 mmol, 1 equiv.), aryl amine (0.5 mmol, 5 equiv.) and aliquot from stock solution (125 µL). The vials were sealed with a teflon cap, removed from the glove box, and heated to 120 °C for the specified time. The resulting slurry was then cooled to room temperature, the 4 mL vial was uncapped, diphenylmethane (5 µL, 30.0 µmol) was added as an internal standard, and *ca* 1 mL each of half-saturated K_2CO_3 (aq) and $CHCl_3$ was added to the slurry. The 4 mL vial was capped, the biphasic mixture shaken several times, and then sonicated for 15 minutes. The crude organic layer was analyzed in duplicate by gas chromatography. Relevant data is summarized below.





Aniline	Run	Slope	Standard Error
	**1**	$3.66*10^{-3}$	$1.89*10^{-4}$
	2	$3.54*10^{-3}$	$3.23*10^{-4}$
	3	$2.54*10^{-3}$	$9.30*10^{-4}$
	**1**	$1.83*10^{-3}$	$7.06*10^{-5}$
	2	$2.52*10^{-3}$	$5.97*10^{-4}$
	3	$1.98*10^{-3}$	$2.74*10^{-4}$
	**1**	$1.46*10^{-3}$	$2.04*10^{-4}$
	2	$1.54*10^{-3}$	$3.21*10^{-4}$
	3	$1.25*10^{-3}$	$2.48*10^{-4}$
	**1**	$2.80*10^{-3}$	$3.27*10^{-4}$
	2	$2.15*10^{-3}$	$6.60*10^{-5}$
	3	$2.11*10^{-3}$	$2.96*10^{-4}$
	**1**	$3.28*10^{-3}$	$2.68*10^{-4}$
	2	$2.63*10^{-3}$	$2.65*10^{-4}$
	3	$2.44*10^{-3}$	$1.89*10^{-4}$

4.9 References

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